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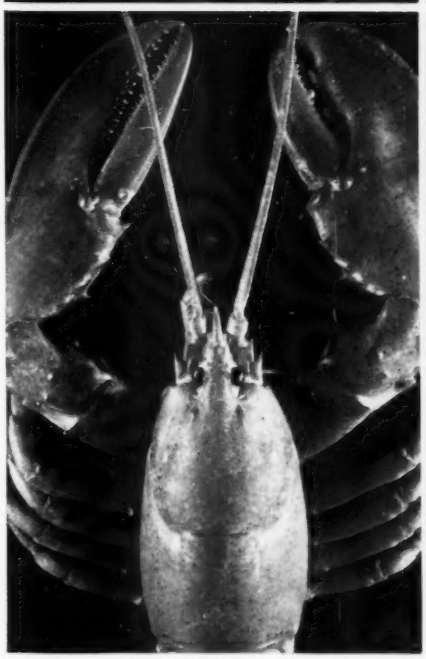

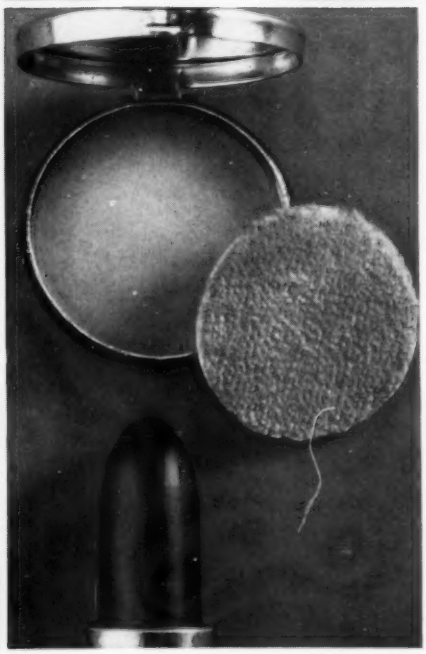

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MEETINGS *and Postgraduate Courses*

AMERICAN INSTITUTE OF BIOLOGICAL SCIENCES, LAFAYETTE, INDIANA: The annual joint meeting of biological societies will be held at Purdue University, August 27-September 1. For further information, write to: Harold F. Osborne, Director, Biology News Bureau, American Institute of Biological Sciences, 2000 P St., N. W., Washington 6, D. C.

INTERNATIONAL UNION OF THERAPEUTICS, GENEVA, SWITZERLAND: Seventh annual congress to be held at the University of Geneva, October 6-8. For further information, write to: Dr. P. Rentchnick, Case Postale 229, Geneva 4, Switzerland.

INTER-SOCIETY CYTOLOGY COUNCIL, MEMPHIS: Annual scientific meeting to be held at Hotel Peabody, November 2-4. For further information, write to: Dr. Paul A. Younge, Secretary-Treasurer, 1101 Beacon Street, Brookline 46, Mass.

NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND: Eleventh annual symposium on recent developments in research methods and instrumentation to be held October 9-12. For further information, write to: Mr. James B. Davis, Executive Secretary, National Institutes of Health, Bethesda 14.

UNIVERSITY OF COLORADO SCHOOL OF MEDICINE, DENVER: Postgraduate course in external ophthalmology to be held at the Stanley Hotel, Estes Park, Colorado, July 10-13. For further information, write to: Office of Postgraduate Medical Education, University of Colorado Medical Center, 4200 East Ninth Avenue, Denver 20.

UNIVERSITY OF LOUISVILLE MEDICAL SCHOOL, LOUISVILLE: Postgraduate courses for 1961:

Medicine, July 13, Harrodsburg
Obstetrics, October 5, Paducah
X-ray interpretation, October 5-December 21 (Thursday nights), Louisville General Hospital
Recent advances in therapeutics, October 19, Pikeville
Anesthesiology, October 19
Clinical neurology, November 16, Louisville General Hospital
Norton Memorial Infirmary seminar, December 14

A one week course in obstetrics and gynecology will be held every week for the remainder of the year at the Louisville General Hospital, with the exception of October 2-7 and October 23-28. Enrollment is limited to two physicians each week. For further information, write to: Dr. Friedrich Hertle, Executive Director, Postgraduate Medical Education Office, 104 West Chestnut Street, Louisville 2.

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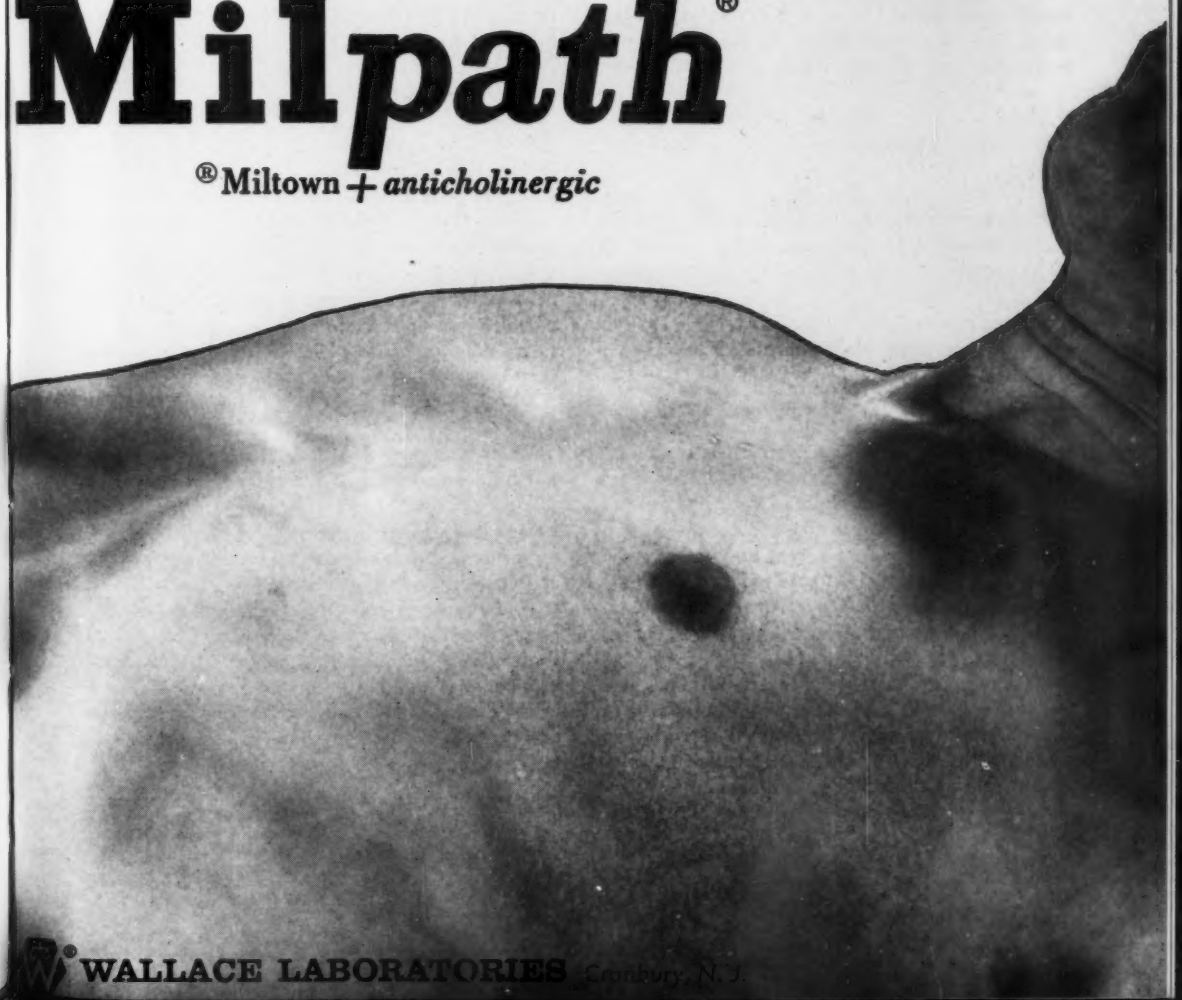

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants. Replies are forwarded by mail immediately and selected questions and answers are published each month in this section.

• THIO-TEPA

Several inquiries have been received recently regarding the use of thio-TEPA or TSPA in the treatment of cancer. For comprehensive information on the use of these agents, it is suggested that inquiries be directed to the Cancer Chemotherapy National Service Center at the National Cancer Institute, Bethesda, Maryland. The Center maintains a file of bibliographic information on the subject of chemotherapeutic agents and can furnish the most current information in this field.

• THE EXECUTIVE EXAMINATION

Q. What routine laboratory tests and x-ray studies are recommended for routine periodic examinations of company executives more than 40 years of age? Should gallbladder visualization, gastrointestinal x-rays, barium enema studies or proctoscopy be performed even though symptoms are minimal or nonexistent?

M.D.—California

A. There is a divergence of opinion among internists as to whether roentgenographic studies of the gastrointestinal tract should be done as part of an annual routine checkup. Generally speaking, in the absence of pertinent symptoms, such procedures are unnecessary and undesirable. However, most physicians agree that proctoscopy should be included in the general examination. If rectal polyps are discovered, a roentgenogram of the colon should then be made.

Many companies request that additional gastrointestinal studies be made in periodic examinations; however, as a rule, such requests are stimulated by the finding of an unsuspected malignant process or some occult illness among personnel of the company which is concerned.

It is preferable to allow the examining physician great latitude in his judgment of the indications for gastrointestinal or other studies during the course of an annual routine health examination. The best medical care is afforded when laboratory and roentgenographic studies are selected on the basis of the indications from a carefully taken history and a carefully conducted physical examination.

• NOCTURNAL ERECTION

Q. A 45 year old man is awakened two to three hours after falling asleep at night by an erection which is unrelated to sexual intercourse and is accompanied by a desire to urinate. The patient is unable to sleep following this occurrence.

Urologic investigation revealed minimal prostatic hypertrophy but treatment with massage did not alleviate the condition.

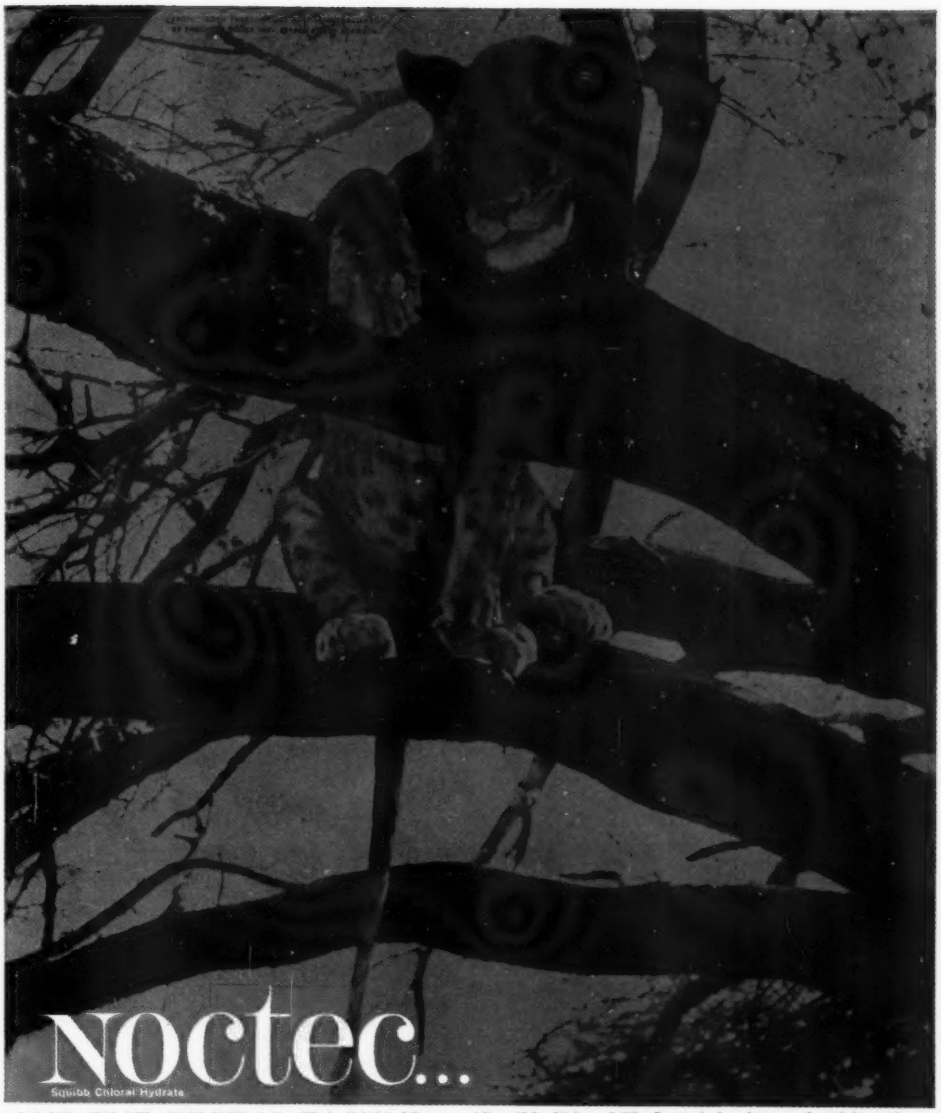
What is the cause of this condition and what treatment would you suggest?

M.D.—California

A. The cause of these nocturnal erections cannot be determined without more data regarding this man's sexual habits during adolescence and before and during marriage and his present entertainment, social contacts, etc. Neuropsychiatric consultation is advisable.

If the condition is not controlled by psychiatric treatment, 1 gr. of stilbestrol and a mild tranquilizer taken at bedtime may be effective. The patient should be informed that the estrogen may reduce sexual desire while it is being used and that the dosage may have to be increased to produce the desired effect.

(Continued on page A-18)



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• LEUKEMIA AND PRIMARY POLYCYTHEMIA

Q. Should the level of alkaline phosphatase be considered in the differential diagnosis of leukemia and primary polycythemia?

M.D.—Ohio

A. The alkaline phosphatase content in the leukocytes often is low in the presence of chronic myelocytic leukemia, while it may be elevated in some cases of primary polycythemia, particularly when leukocytosis also exists. The content also may be increased in the presence of myeloid metaplasia, although it varies considerably in this condition. In a variety of other hematologic diseases, low values for alkaline phosphatase have been observed. In the presence of pyogenic infections the values may be high.

Determination of the content of alkaline phosphatase in the leukocytes is an interesting and suggestive adjunct to the differential diagnosis of chronic myelocytic leukemia and primary polycythemia, but it is not exclusively definitive.

A good discussion of this problem can be found in the report of K. R. Tanaka, W. N. Valentine and R. E. Fredricks, which deals with diseases associated with low leukocyte alkaline phosphatase. (New England J. Med. 262:912-918 [May 5] 1960.)

• DIETARY FLUORIDES

Q. If fluoridation of the general water supply is unfeasible, what is the best method of administering fluorides to children of elementary school age? What is the proper dosage, and how are fluorides best prepared for a large group?

M.D.—Tanganyika

A. Although the fluoridation of water supplies has proved valuable, there is less evidence concerning the value of sodium fluoride as a dietary supplement. It may be assumed a priori, however, that such supplementation is beneficial to persons living in localities where community fluoridation programs are not available.

The Council on Dental Therapeutics of the American Dental Association has recommended supplementing the diet with fluorides under professional supervision. For dietary supplementation the suggested method is to administer 2.2 mg. tablets of sodium fluoride to children on the following bases: (1) If the child is less than two years old, add 1 fluoride tablet to each quart of water used for drinking and for preparing formulas and other foods. (2) If the child is two to three years old, give 1 fluoride tablet on alternate days in a glass of fruit juice or drinking water. (3) If the child is more than three years old, administer 1 tablet daily in a glass of fruit juice or drinking water.

If it is more convenient, 0.132 gm. of sodium fluoride may be added to 240 gm. of distilled water, and 1 teaspoonful may be used on the same bases as the 2.2 mg. tablets. These quantities are to be given when the natural water supply is devoid of fluoride. The amount of fluoride may be adjusted downward by 10 per cent for each 0.1 part per million of fluoride ion in the water supply. For further details, see the report of the Council on Dental Therapeutics of the American Dental Association on prescribing supplements of dietary fluorides (J. Am. Dent. A. 56:589-591 [April] 1958).

• APHASIA AND APRAXIA

Q. The parents of a three year old boy are concerned about his mental development. The child's weight and height are normal for his age, and there is no evidence of cranial nerve dysfunction or of pyramidal, extrapyramidal or cerebellar disturbance. The only positive findings are inability to enunciate and understand words (aphasia) and to execute simple commands (apraxia).

The child's past history is significant. At 18 months of age, when his speech, comprehension and motor coordination were normal, he had meningo-encephalitis of undetermined cause.

Can this child benefit from speech therapy? If so, what centers offer this training?

M.D.—Jamaica

A. Inability to enunciate and understand words and to execute simple commands suggests serious focal brain damage. This is probably the result of the meningo-encephalitis. The possibility of partial or total deafness also should be considered, since a deaf child might present the symptoms described.

The value of speech therapy in this case would depend on the definitive diagnosis, which is the most compelling need at the moment. Any major university medical center usually provides facilities for speech therapy.

What's happening in Medicine ?

POSTGRADUATE MEDICINE'S REPORT of late news of interest to practicing physicians

X-RAY EXAMINATION DURING PREGNANCY

American College of Obstetricians and Gynecologists, Miami Beach:

• More lives probably could be saved by appropriate x-ray examination during pregnancy than are likely to be lost or even affected by irradiation to the unborn baby. Statistics on mothers who died in childbirth, babies who were stillborn, and infants who died shortly after birth show that the hazards would be greatly reduced by appropriate x-ray examinations during pregnancy to diagnose difficult problems. Such examinations should be conducted as late in pregnancy as possible, and the need for them definitely established.—Dr. Ruth Quimby, Columbia University College of Physicians and Surgeons, New York.

• Planning produced 45 per cent more live babies than earlier unplanned pregnancies among the same group of 77 women. The group had previously lost 52 per cent of unplanned babies. Through planned therapy, the proportion of live births rose from 48 per cent to 69.7 per cent.—Dr. A. F. Goldfarb, Philadelphia.

CORTICOSTEROIDS IN CHILDREN

American Academy of Pediatrics, Washington, D. C.:

• Although varying degrees of growth arrest may be seen in children receiving corticosteroids, growth spurts occur following discontinuation of therapy. Low-dosage corticosteroid therapy is compatible with relatively good growth rates. Indiscriminate discontinuation of therapy may endanger life by causing a full-blown toxic crisis. For this reason, parents must be made to understand that a child receiving corticosteroids must take the drugs regularly and on schedule. A break in the schedule may be courting disaster.—Dr. Thomas A. Good, University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore.

• Less than a tablespoonful of salt will severely poison even a healthy infant. While not a common occurrence, severe poisoning by common table salt may lead to severe brain damage or even death.—Dr. Laurence Finberg, Johns Hopkins University School of Medicine, Baltimore.

• Subtle neurologic deficits, not detectable by the usual neurologic examination even when properly performed, may be etiologically related to certain behavior disorders, language problems, and learning disabilities in children of normal intelligence. Psychologic testing may yield positive evidence of organic dysfunction, although results of the classic neurologic examination are negative. —Dr. Raymond L. Clemmens, University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore.

HOME VISITS IN ALLERGY CASES

American College of Allergists, Dallas:

- Treatment of the family as well as of the patient is entailed in successful allergy therapy. The home visit gives the physician a chance to explain fully the need for environmental precautions. Important sources of difficulty which the patient forgot to mention during office consultation are often discovered.—Dr. Joseph R. Wiseman, Syracuse.
- Allergic patients may have gastrointestinal symptoms simulating gallbladder disease, ulcer or appendicitis. Inhalants, antibiotics and various foods may be at fault.—Dr. Orval R. Withers, University of Kansas Medical Center, Kansas City.

DIETS AND SERUM LIPID LEVELS

Federation of American Societies for Experimental Biology, Atlantic City:

- Serum lipid levels were compared in four age-matched dietary groups. Korean soldiers given a 3600 calorie diet with 15 per cent fat content (12 per cent vegetable fat) had significantly lower levels than United States soldiers given a 4500 calorie diet with a 42 per cent fat content (29 per cent animal fat). Korean Buddhist priests on a strict vegetarian diet of 2600 calories (7 per cent vegetable fat) had slightly lower serum lipid levels than the Korean soldiers. —Dr. K. T. Lee, Albany Medical College of Union University, Albany, N. Y.
- Desoxyribonucleic acid (DNA) from human and other mammalian sperm has been isolated in biochemically intact form for the first time. While DNA can be isolated easily from the sperm of fish and lower vertebrates, such an isolation from mammalian sperm has hitherto been extremely difficult, if not impossible.—Dr. Ellen Borenfreund, Sloan-Kettering Institute for Cancer Research, New York.

ADJUVANT DRUG CUTS CANCER RECURRENCE

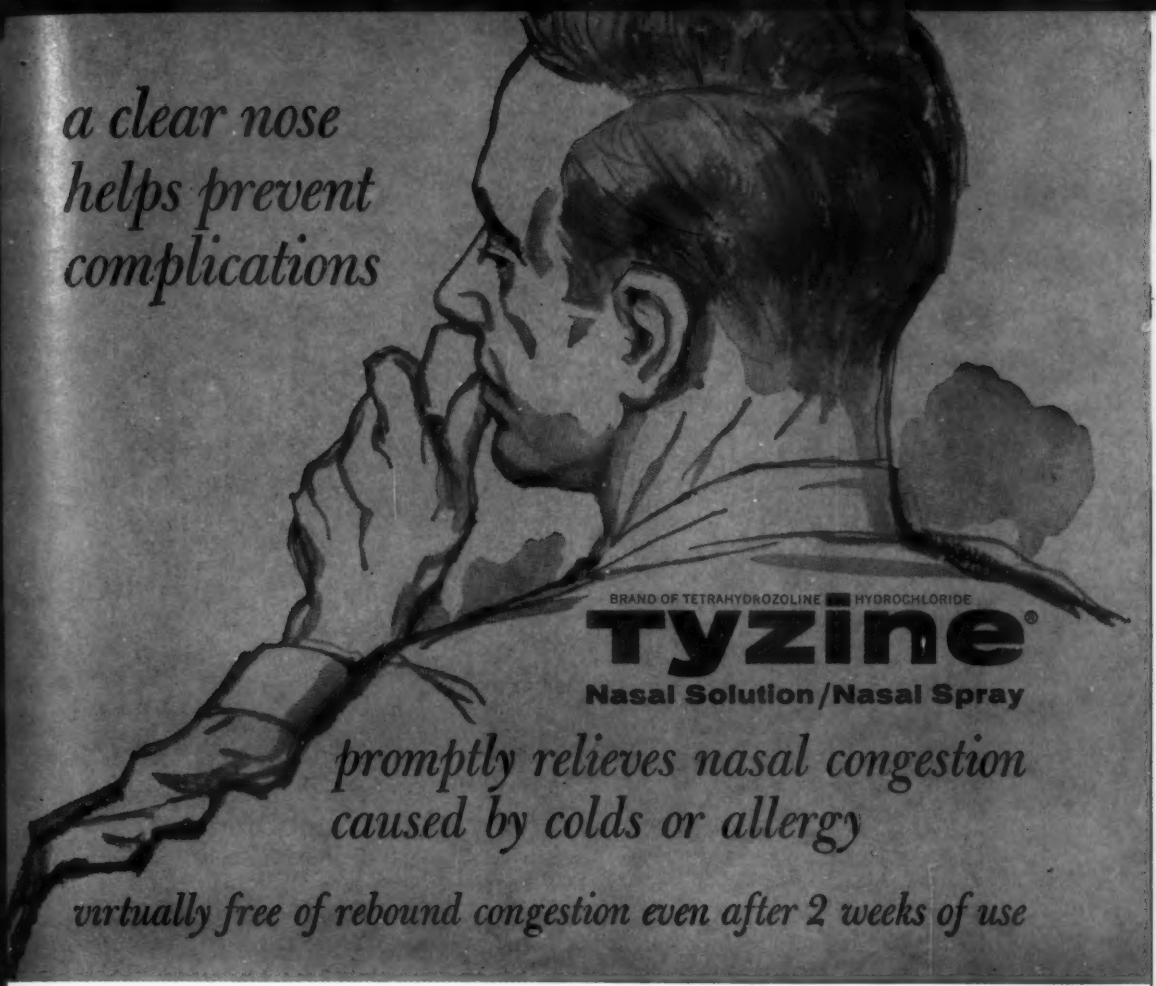
American Surgical Association, Boca Raton, Fla.:

- Data so far accumulated indicate that a statistically significant decrease occurs in the early recurrence rate among some groups of patients receiving triethylenethiophosphoramide (thio-TEPA) as an adjuvant to radical mastectomy. Among 108 patients receiving the high dosage (0.8 mg. per kilogram of body weight), the recurrence rate was 22 per cent for the first 35 months, compared with 44 per cent among those treated with radical mastectomy alone. In the low-dosage group (0.6 mg. per kilogram of body weight), recurrences appeared in 7 per cent, compared with 11 per cent among controls.—Dr. Rudolph Noer, University of Louisville School of Medicine, Louisville.
- Electrohemostatic measures have been effective in stopping uncontrollable bleeding in splenic rupture, brain surgery, amputations and gunshot wounds.— Dr. P. N. Sawyer, State University of New York Downstate Medical Center, Brooklyn.
- High cervical chordotomy is a practical means of relieving pain in malignancy, but it will be ineffective if the patient has become seriously addicted to pain-relieving drugs before surgery.—Dr. Douglas Hawkes, Memphis.

THE INFORMED CONSENT

Medicolegal Conference, San Francisco:

- The era of oral consent in surgery is past. Oral explanations will not suffice because the "forgetful" patient might later deny that such explanations were made. The written consent is mandatory and must be complete, intelligent and informed, with an understanding of what is to be done and the risks involved.—Dr. Leo J. Adelstein, Los Angeles.



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Important: Use TYZINE Pediatric Nasal Drops (0.05%) for children under 6 years. The 0.1% concentration is contraindicated in this age group.

SIDE EFFECTS: Transient mild local irritation after instillation has been reported in rare instances.

PRECAUTIONS: Avoid doses greater or more frequent than those recommended above. Use with caution in hypertensive and hyperthyroid patients.

Overdosage may cause drowsiness, deep sleep, and, rarely, marked hypotension in infants and young children. KEEP OUT OF HANDS OF CHILDREN OF ALL AGES.

SUPPLIED: *Nasal Solution,* 1-oz. dropper bottles, 0.1%. *Nasal Spray,* 15 cc., in plastic bottles, 0.1%. *Pediatric Nasal Drops,* ½-oz. bottles, 0.05%, with *calibrated* dropper.

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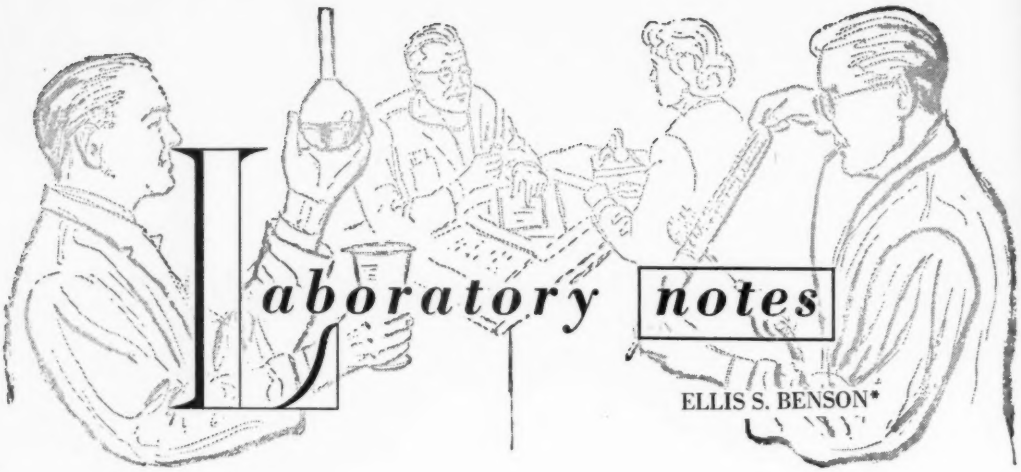

ELLIS S. BENSON*

An Enzymatic Defect in Drug-Sensitive Hemolytic Anemia

A RECENT chain of experimental findings in the study of certain drug-sensitive anemias has shed new light on some puzzling hemolytic anemias and provides a mechanism of investigation into the biochemical economy of the erythrocyte. The manner in which this has taken place is both interesting and instructive.

The occurrence of hemoglobinuria accompanying malaria long has been known as "blackwater fever." Its sudden onset, symptoms (chills, fever, pain in loins), signs (dark urine followed by icterus), and self-limited course are characteristics of an acute hemolytic episode.[1] The mechanism of this occurrence is obscure, but among the precipitating agents are antimalarial drugs. Similarities have been noted with favism, an acute hemolytic anemia occurring in peoples of the Mediterranean littoral following the ingestion of the broad bean *Vicia fava*.

The so-called blanket treatment of malaria by the British army in India and Burma in the 1940s[2] and the radical treatment used by the United States army in Korea in 1950[3] were attempts to treat curatively persons moving from a malarial area to a nonmalarial one and thus meet the problem produced by the constant threat of relapse. The only class of drugs which acted by destroying the tissue stages of the disease and were thus curative were members of the 8-aminoquinoline family, notably, pamaquine and primaquine. These two drugs were used together with suppressive agents in the blanket[2] and radical[3] regimens. Hemoglobinuria and acute hemolysis were early noted to be among the hazards of 8-aminoquinoline therapy.[4]

In 1944, Alving and associates began a program of investigation on the use of antimalarial agents in volunteers at Statesville Penitentiary, Illinois.[3] During the course of this study, a series of observations were made which had quite unexpectedly broad and fundamental significance.[5]

By 1954, when the first of these observations was reported, it had been recognized that 8-aminoquinoline-induced anemia occurred as an acute hemolytic process in a small group of susceptible individuals who were primarily of non-European origin.[2,3]

(Continued on page A-40)

*Director of Hospital Laboratories and Associate Professor of Clinical Laboratory Medicine and of Pathology, University of Minnesota Medical School, Minneapolis, Minnesota.

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1. Lapan, B.: Am. J. Obst. & Gynec. 78:1320, 1959. (156 patients)
2. Breen, J. L.: Obst. & Gynec., to be published. (39 patients)
3. Nathanson, E. A.: Obst. & Gynec. 16:601, 1960. (100 patients)
4. Mendel, E. B.: Am. J. Obst. & Gynec., to be published. (109 patients)

Ortho

Candida Albicans grown on Nickerson's® Medium; photograph supplied by Dr. A. B. Kupferberg of Ortho Research Foundation.

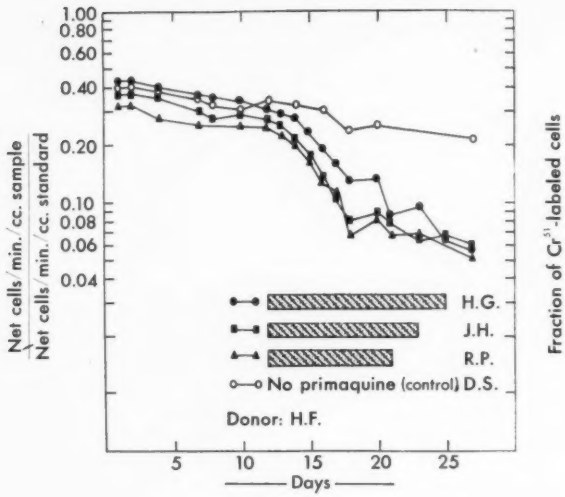

FIGURE 1. Fate of red blood cells from a primaquine-sensitive donor transfused into normal volunteers (solid symbols) who were then given primaquine on the days indicated, and into a normal volunteer (open symbols) who was not given primaquine. Note increased rate of disappearance of tagged red blood cells when primaquine was given.

(Reproduced from Dern et al.[6] with permission from The C. V. Mosby Company.)

The following observations were made by the Chicago (Statesville) group:

1. In 1954, Dern and associates[6] reported the results of a study of survival of radioactive chromium-tagged red blood cells. When tagged red blood cells of a primaquine-sensitive donor were transfused into normal recipients, administration of primaquine to the recipients resulted in a sharply increased rate of disappearance of tagged cells (figure 1), indicating hemolysis of the injected cells. The same rate of hemolysis was noted in a recipient who previously had had a splenectomy. Red cells of normal donors were not lysed when infused into primaquine-sensitive recipients who were receiving the drug. These observations indicated that primaquine-sensitive hemolysis was due to an intrinsic defect of the red blood cells present in susceptible individuals.

2. Further studies of red cell survival indicated that after drug-induced hemolysis had gone on for 8 to 10 days, it ceased, even though administration of the drug (primaquine) continued.[7] Apparently, a reduced sensitivity of the red cell population developed. Beutler, Dern and Alving[8] then studied the effect of red cell age on drug sensitivity. Red cells of a narrow age range from a primaquine-sensitive individual were labeled with radioiron and infused into a normal recipient. When the labeled erythrocytes were 8 to 21 days old, administration of primaquine did not induce their hemolysis. When they had reached the age of 75 to 85 days, they were rapidly destroyed on administration of primaquine. Thus, the inherent defect of the red cells associated with primaquine sensitivity was clearly a function of red cell age and was more pronounced in older cells.

The self-limited nature of the drug-induced hemolysis noted by Dern, Beutler and Alving[7] probably is explained in this age effect.

3. No differences were noted between primaquine-sensitive erythrocytes and those of normal individuals with respect to osmotic, mechanical and chemical fragility.[9] Erythrocyte morphology, too, was similar except in one respect: In primaquine-sensitive individuals Heinz bodies appeared before and during a hemolytic episode.[9] Heinz bodies are small, dense intracellular particles seen in stained preparations of red cells in a variety of toxic conditions.[10] Formation of Heinz bodies may be induced in vitro by a number of agents added to blood,[10] and Beutler, Dern and Alving,[11] using acetylphenylhydrazine as the inducing agent, found that this in vitro formation of Heinz bodies was more pronounced in primaquine-sensitive erythrocytes than in normal ones. Since this process was markedly

(Continued on page A-42)

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affected by the degree of oxygenation, the attention of these workers turned to erythrocytic mechanisms of oxidation-reduction and to glutathione (GSH).[12]

Although the precise role of GSH in the economy of the red cell is obscure, it is very likely related to its ability as a reducing substance, a hydrogen donor. At any rate, Beutler et al.[12] examined its concentration in primaquine-sensitive erythrocytes and found it to be distinctly lower than in normal red cells. Later, Flanagan et al.[13] found that primaquine administration in primaquine-sensitive individuals was followed by a sharp fall in erythrocyte GSH and, in turn, acute hemolysis. Thus, the search for an inherent defect in the red cells in primaquine-sensitive hemolytic anemia led to clear evidence of a biochemical abnormality in such cases.

4. Among the reactions taking place in red blood cells in which GSH participates are the following:*

$$\text{I. GSSG} + \text{TPNH} + \text{H}^+ \rightleftharpoons 2\,\text{GSH} + \text{TPN}^+$$

$$\text{II. G-6-P} + \text{TPN}^+ \rightleftharpoons \text{6-P-G} + \text{TPNH} + \text{H}^+$$

$$\text{III. 6-P-G} + \text{TPN} \rightleftharpoons \text{Pentose phosphate and } CO_2 + \text{TPNH} + \text{H}^+$$

Reaction I is catalyzed by the enzyme glutathione reductase, reaction II by glucose-6-phosphate dehydrogenase, and reaction III by 6-phosphogluconate dehydrogenase. In 1956, Carson and associates[14] reported assays of each of these three enzymes in hemolysates of primaquine-sensitive and nonsensitive erythrocytes. The results are illustrated in figure 2. Clear evidence of deficiency in glucose-6-phosphate dehydrogenase activity of primaquine-sensitive cells is seen.

In Carson's[5] words, "The excitement of this discovery quickly shifted to the questions raised rather than those answered." Many of these questions remain unanswered, notably: What is the mechanism of the hemolysis? What links the enzyme deficiency with the hemolysis? The answers to these questions will cast interesting light on the biochemical economy of the red blood cell. This aspect of the problem is discussed in Carson's[5] review.

From the practical standpoint, the discovery of the enzymatic defect led to assay methods which are useful in the diagnosis of hemolytic disturbances.[15,16] The observations of Beutler et al.[12] and Flanagan and associates[13] on the GSH content of drug-sensitive erythrocytes and the induction of formation of Heinz bodies in these cells by acetylphenylhydrazine[11] were the bases of an assay known as the GSH stability test, [16,17] which appears to detect sensitively the enzymatic defect.[16]

Application of these tests to the study of hemolytic disturbances has brought some interesting revelations. It soon became apparent that red cells with the primaquine-sensitive type of biochemical defect were sensitive to a number of other agents known to be inducers of acute hemolysis. Among the agents implicated have been sulfanilamide, acetanilid, phenacetin, naphthalene and para-aminosalicylic acid.[16,18]

Favism was soon studied and found to be based on the same red cell defect as that in primaquine sensitivity.[19,20] Glucose-6-phosphate dehydrogenase red cell deficiency also has been found in children with chronic congenital nonspherocytic anemia.[21,22] Recently, the defect has been described in infants in Singapore and in Greece who have severe neonatal jaundice in which iso-immunization can be excluded.[23,24] The relation of these cases to the drug-sensitive hemolytic disease group is not yet entirely clear.

Considering anew the problem of so-called blackwater fever and reflecting on the observation that it does not develop in adult inhabitants of an endemic malarial region as long

(Continued on page A-44)

*The following abbreviations are used: GSH, reduced glutathione; GSSG, oxidized glutathione; TPNH, reduced triphosphopyridine nucleotide; TPN, oxidized triphosphopyridine nucleotide; G-6-P, glucose-6-phosphate; 6-P-G, 6-phosphogluconate.

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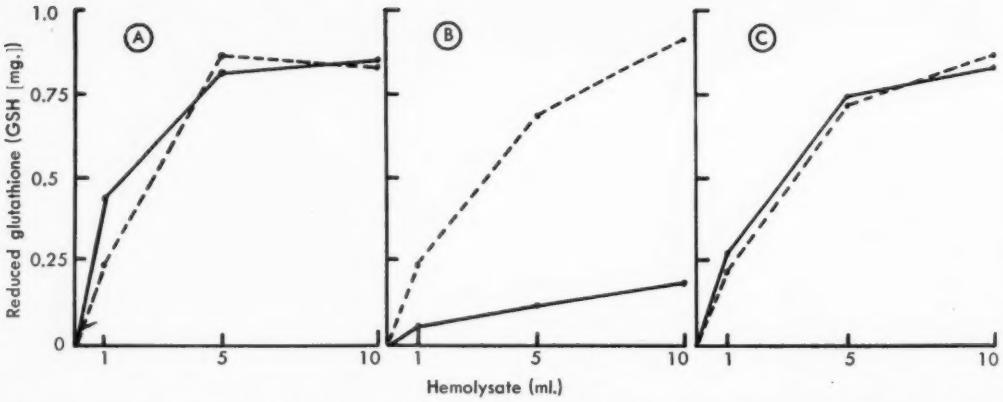

FIGURE 2. Milligrams of reduced glutathione (GSH) formed from oxidized glutathione (GSSG) as a function of milliliters of dialyzed hemolysate. Solid curve, primaquine-sensitive subject; dashed curve, normal subject. A. Assay of GSH reductase activity (reaction I). B. Assay of G-6-P dehydrogenase activity (reactions II and I). C. Assay of 6-P-G dehydrogenase activity (reactions III and I).

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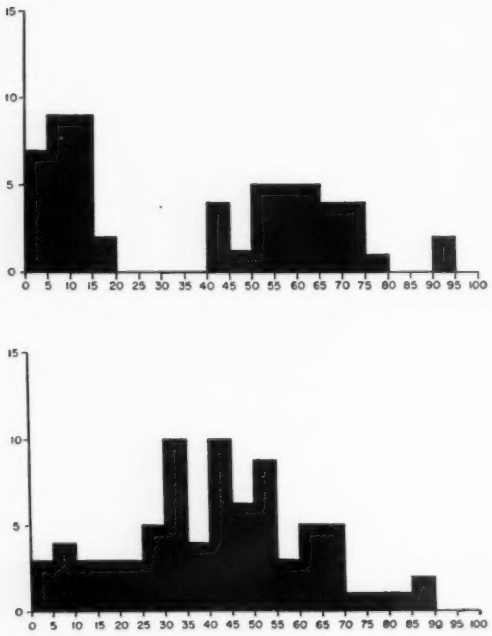

FIGURE 3. Distribution of postincubation glutathione values (in glutathione stability test[17]) among members of 16 families. Upper graph, men; lower graph, women. Ordinates, number of individuals. Abscissas, postincubation glutathione in milligrams per 100 ml. packed red cells.

(Reproduced from Childs et al.[28])

as they remain undisturbed in their endemic environment, Gilles and Ikeme[25] reported three cases of blackwater fever in adult Nigerians with glucose-6-phosphate-deficient red cells. In these cases, drug sensitivity was indictable.

Striking differences in susceptibility between American Negroes and white persons have been noted, the incidence of the defect being much higher in the former group.[4,26] An incidence as high as 20 per cent has been reported from Nigeria.[25] It is relatively common among peoples of the Mediterranean area, especially in certain islands (Sardinia, for example), perhaps because of geographical isolation.[5] In Israel, the defect is much more common in Sephardic (Asiatic) than in Ashkenazic (European) Jews, and it reaches its highest incidence there among certain heavily inbred families from Iraq.[19] Interestingly, it was among these people that Lederer[27] found what he termed "Baghdad spring anemia," an acute hemolytic disturbance which he ascribed to exposure to the pollen of certain blossoms, including those of *V. fava* (and in some cases ingestion of the beans of this plant as well). Carson[5] estimates that there are 100 million people with the primaquine-sensitive type of red cell defect.

(Continued on page A-46)

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Childs and associates[28] have worked out the mode of genetic distribution of the defect, using the GSH stability test.[16] The incidence of the defect among men was found to be 14 per cent, and among women it was 2 per cent. In addition, 5 per cent of the women tested showed partial sensitivity (intermediate range between normals and drug-sensitive groups with respect to GSH stability). Figure 3 illustrates the distribution of postincubation GSH values in families in which the defect had been found. A postincubation value of 22 mg. GSH per 100 ml. packed cells or less was considered to be evidence of the presence of the enzymatic defect. These individuals are termed "reactors." Note that while in the male family members the values fall nicely within two groups, normals and reactors, among female members there are many intermediate values. These findings fit best the hypothesis that the mode of inheritance is by a sex-linked gene having incomplete dominance.

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Radiology FOR PRACTICING PHYSICIANS

PAUL C. HODGES*

Radiology in Free China

DIAGNOSTIC radiology got off to an early start in China. In February 1895, at the close of the Sino-Japanese War and nine months before the discovery of x-rays, the imperial premier of China, Li Hung-chang, while representing his country at peace negotiations in Japan, was shot in the cheek by a would-be assassin. Fourteen months later he journeyed to Russia and Germany by trans-Siberian railway and, on returning home by way of England and the United States, brought with him a German x-ray plate which almost certainly was the first ever to reach the Orient and which, following his death in 1901, was displayed in the Li family ancestral shrine near Lüchow in Anhwei Province.[1,2]

As late as 1910 and even in America, it was only in cities such as New York, Boston, Philadelphia and Chicago that physicians could expect radiologic help except in the care of fractures, dislocations and gunshot wounds. Even in the field of orthopedics, in which the value of x-ray plates was widely recognized, cities as large and progressive as Madison, Wisconsin, only recently had developed adequate facilities. It is not surprising, therefore, that when I first saw Shanghai in 1915, except for an experienced and gifted British radiologist who was doing excellent work at the Shanghai General Hospital, I found either no radiology at all or a mere token variety throughout the Yangtze Valley. In the eight years following 1919, I was in charge of radiology at the Peking Union Medical College and in that capacity taught the subject to medical students, conducted summer courses for physicians and, with Rockefeller Foundation money (appropriated through its China Medical Board), designed and constructed some 15 small x-ray machines for use in various parts of China. Following my return to America in 1927, the work of the department continued under my former student and senior associate, Dr. C. K. Hsieh, aided during the first year by Dr. Dabney Kerr, who had been one of my summer school students. Hsieh was aided also by my junior student, C. Wu, and later by his own student, T. S. Jung. Later, Dr. Hsieh brought out Dr. Marvin Williams (subsequently a member of the Mayo Clinic staff) to serve for several years as radiologic physicist.

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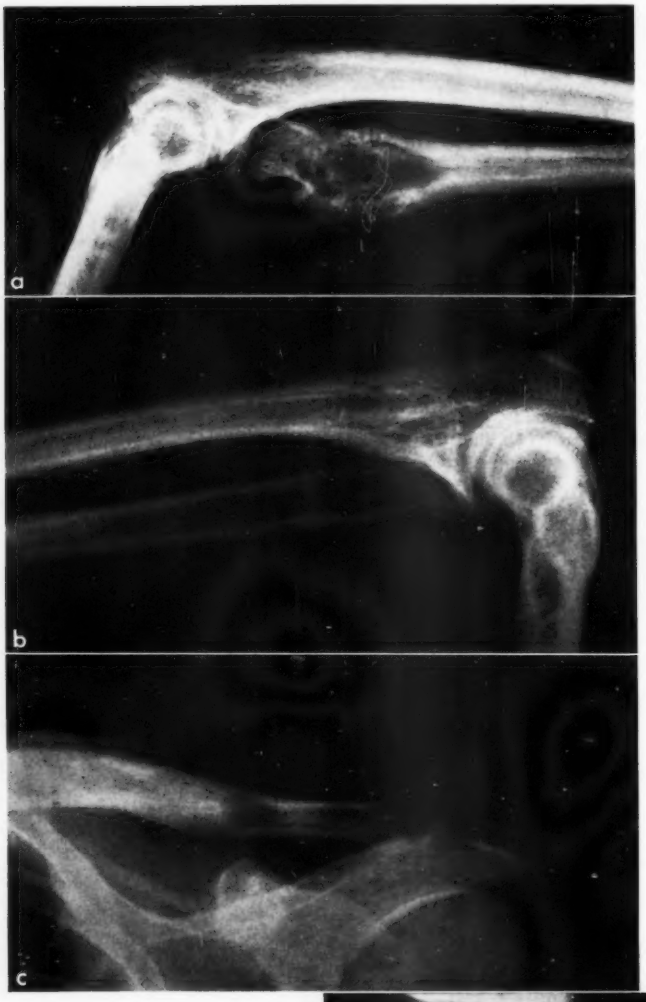

FIGURE 1. a. Lesion of cystic tuberculosis at the proximal end of the left radius in a 61 year old man who was a patient of Dr. Virginia Kuan at the Taiwan Veterans General Hospital.

This patient was known to have had pulmonary tuberculosis 13 years earlier, but at the time of this examination the sputum was negative. He had pain in both elbows, the left knee and the left shoulder.

b and c. Similar lesions were observed in the right radius (b) and in the left clavicle (c). Lesions also were present in the right tibia and fibula and in the skull. Biopsy of the two radii confirmed the diagnosis of tuberculosis. The patient recovered with chemotherapy.

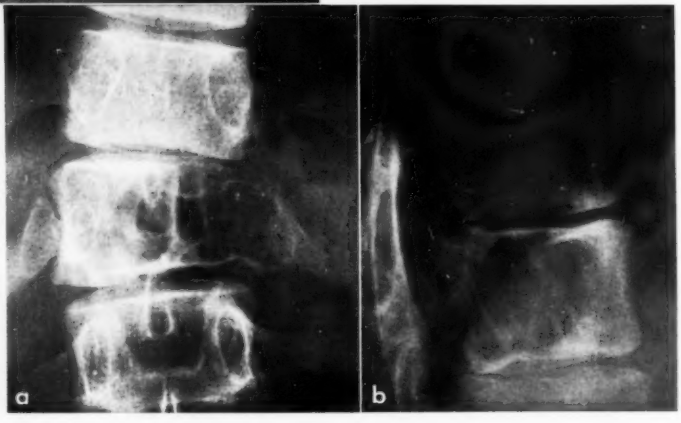

FIGURE 2. a and b. Frontal and left lateral views of a giant-cell tumor of the vertebra involving the twelfth thoracic vertebra and the left twelfth rib in a 27 year old man. This patient was seen by Dr. L. C. Chiang, National Taiwan University Hospital.

Jaffe[4] believes that most so-called giant-cell tumors of the vertebrae are, in fact, aneurysmal bone cysts, but the radiologists and pathologists at the Hospital are convinced that this particular lesion actually was a giant-cell tumor.

In the hopeful early years of the Nationalist Government, Dr. J. Heng Liu and his associates, recognizing that radiology was essential to the practice of medicine and surgery, developed it as rapidly as possible in the face of endless other pressures on funds and man power. With the advent of the war with Japan, Dr. Robert Lim's hard-pressed military physicians somehow managed to maintain a barely adequate radiologic service, the work being expedited by funds donated by the American Bureau for Medical Aid to China, Inc., and by apparatus selected, gathered and forwarded by Dr. Liu. With the fall of the mainland to the Communists, some, but, unfortunately, only a few, of the abler radiologists managed to get out to Taiwan and to take with them a tiny amount of equipment. From that seed there has grown in the past decade much of the best of Taiwan's present-day radiology.

X-ray Diagnosis

The single most potent factor in superior x-ray diagnosis of skeletal lesions is cooperation among orthopedic surgeons, radiologists and skillful, experienced bone pathologists. Even the United States has developed few Phemisters, Jaffes and Hatchers; Taiwan has no experienced personnel in this field, and, as a result, the skeletal phase of x-ray diagnosis languishes there. The situation is a little better in x-ray diagnosis of peptic ulcer and gastric neoplasm, although that field is hampered by rather clumsy facilities for gastric spot filming. Pyelography and cholecystography are not as good as they could be if better contrast media were available, and examination of the skull is hampered by the lack of special skull stands and the almost universal failure to employ stereoscopy. Most examinations of the esophagus and colon are well done, but the Chinese excel particularly in diagnosing diseases of the chest; they do it in spite of a rather poor average quality of films and infrequent use of grids or stereoscopy. The explanation lies in the availability of a prodigious amount of material and in the cooperation among radiologists and unusually capable pathologists, internists and thoracic surgeons. Tuberculosis is tragically prevalent,

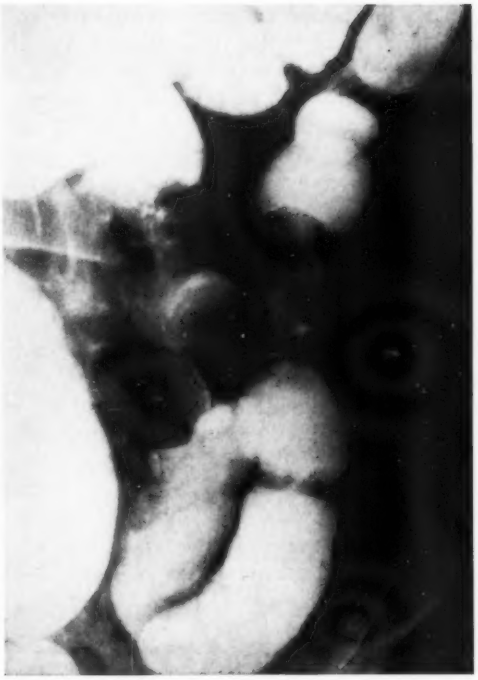

FIGURE 3. Carcinoma of the colon with fistulous communication between adjacent bowel loops in a 60 year old diabetic man seen by Dr. L. C. Chiang.

This patient passed large amounts of red blood three years earlier and again just before the hospitalization during which this x-ray was made. He had no other symptoms.

bronchiectasis far from infrequent, pulmonary neoplasm at least as common as in the United States, and paragonimiasis always an interesting possibility;[3] however, histoplasmosis, it is said, has never been found on the island.

Personnel

For approximately 10 years there have been training programs in radiology at Taita, medical college of National Taiwan University, and the National Defense Medical Center (NDMC), each institution having turned out approximately 15 radiologists. At Taita, the chief is Dr. L. C. Chiang, who has had extensive radiologic training at the University of Pennsylvania. At the NDMC, Dr. C. Wu, now living in the United States, has been succeeded by Dr. H. H. Hou, who had a year of

surgery in Chicago and five years of radiology in Belgium, and by Dr. T. C. Chiang, a graduate of the NDMC, who studied radiology at the University of Pennsylvania for a year. Both institutions have on their staffs several other radiologists with foreign training ranging from one to five years which was acquired in England or at various places in the United States.

The radiology of the Taiwan Veterans General Hospital is in charge of Dr. Virginia Kuan, who received her training at the NDMC and then studied for a year at the University of Pennsylvania. Dr. C. Hsu, who is chief radiologist at the Chinese Air Force Hospital in Taipei, studied radiology for a year at the University of Pennsylvania, and Dr. H. J. Lee, the radiation therapist at the Provincial Hospital in Taipei, studied for three years in the United States and in 1957 was awarded the certificate of the American Board of Radiology. Several other radiologists currently are studying abroad and others are about to embark on such studies.

Illustrative Cases

For two hours each week, radiologists, internists and thoracic surgeons from most of the hospitals and clinics in Taipei meet to discuss diagnostic and therapeutic problems, particularly those concerning thoracic diseases. On one evening a month, the radiologists discuss general radiologic problems. During the six months of my stay, I attended most of these sessions and, in addition, reviewed local films with undergraduate medical students for one hour a week at each of the two medical schools. From among the many hundreds of cases presented at these various sessions I have selected three to illustrate here (figures 1 through 3). I have not included any cases of paragonimiasis because it has recently been discussed in this column by Dr. Watten.[3]

Equipment Problems

Many of those who sell or buy x-ray equipment for use in Taiwan either fail to learn or forget that operating conditions are unlike those in most parts of America or Europe. Electric power (220 V, 60 cycle, AC) is subject to wide fluctuation in voltage; humidity and ambient temperature are high, and public water supplies are meager and frequently rationed or even interrupted. Because of these facts, motor-driven time switches are preferable to those depending on electronic timing circuits, and the best control stands are those having maximal range of adjustability to variations in line voltage. In the matter of developing tanks, the least satisfactory are those in which optimal temperature is maintained by water-cooled compressors supplying a continuous flow of cold water which is mixed with warm water in thermostatically controlled mixing valves.

Radiation Therapy

In Taipei, several institutions have more or less adequate equipment and personnel to provide sound radiation therapy; elsewhere on the island, therapy machines are largely in the hands of nonmedical technicians. Even in Taipei itself, high-class modern radiation therapy remains impossible until facilities can be established to train health and radiation physicists and until there is a continuing supply of radiation therapists. It will be impossible also until there can be established somewhere in Free China a centralized, government-sponsored agency to calibrate and, when necessary, repair instruments for measuring radiation, stipulate the details of radiation barriers, and perform a host of similar functions.

There is reason to hope that the problem of a standardization agency may be solved at Tsing Hua University in Hsinchu, and a therapy training center currently is under construction at the Veterans General Hospital under the supervision of Dr. Nels Strandjord, who is on leave of absence from the University of Chicago and probably will be succeeded by another of our colleagues.

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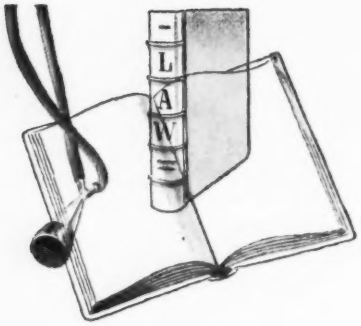

Forensic Medicine

OLIVER C. SCHROEDER, JR.*

Identification of Persons

SAMUEL R. GERBER†

Western Reserve University, Cleveland

Editorial Comment

To identify a person is a real task in legal procedures. But such identification is mandatory. The living person can be identified by interrogation, observation and deduction. The dead person does not respond to interview. Only observation and deduction can be used. Medical practitioners can develop skills to improve this technic of observation and sharpen the deductive process. Furthermore, through detailed medical records, physicians can ease the task of identification. Dr. Gerber shares his knowledge of these matters developed by the experience of single incidents and mass disasters.—Oliver C. Schroeder, Jr.

For law enforcement purposes, the approach and purpose of identifying deceased persons differ in certain respects from the routine identification of living persons. The usual approach to identification of a living person is largely by comparison of descriptions, fingerprints or photographs or by visual recognition. The usual purpose of such identification is to establish that the person in custody is the individual being sought either because of a missing person report or because he has been involved in an offense against society. In either case, the task is simplified when reference fingerprints are available. In these instances, there is seldom any difficulty in obtaining fingerprints of the subject in custody. When there are no reference fingerprints on file, it is necessary to rely on other means of identification such as comparison with descriptions of body characteristics, marks, scars and individual mannerisms which contribute to perceptible recognition.

SAMUEL R. GERBER

The purpose of identifying deceased persons is comparable to identification of living "missing" persons. Legally, the civil implications rather than the criminal aspects are the motivating forces. In most instances, the primary objective in identification of dead bodies is to fulfill humanitarian services or to clarify marital or other legal status of surviving rela-

(Continued on page A-58)

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tives. Questions of inheritance, business contracts, insurance or damage claims cannot be resolved until the death of the individual has been established through valid identification. On some occasions, identification of the dead may be an important factor in criminal cases. For example, identification of a victim of violence facilitates the investigation into his activities and associations prior to death. Also, establishing the fact that a "wanted" person has died is an important aid to clearing police files when the information is forwarded to the proper authorities.

The availability of fingerprint records made during life may simplify but not necessarily assure identification of a dead body. The condition of the body may make it difficult or impossible to obtain fingerprints from the deceased person. Perceptible recognition may be difficult or impossible when such abstract qualities as facial expressions and mannerisms which characterized the individual during life are obliterated by death. In such cases, it is necessary to consider anatomic findings and ancillary evidence offered by clothing, jewelry or other material which may be found associated with the body.

Body characteristics, such as facial features, stature, sex, and color of skin, hair and eyes, are clues to general classifications of both living and dead persons. But, in living persons, traits such as posture, tone of voice, manner of speech, facial expressions, and all sorts of mannerisms characterize the individual and set him apart. These are the factors peculiar to him, so that he is unique—an individual. The conclusion that an individual is recognized by such traits rather than by body characteristics is supported by the fact that descriptions of a missing person frequently are erroneous in regard to color of hair, height, weight and color or type of clothing. However, descriptions are accurate in regard to individual characteristics, such as a limp, grimace, scar or something else that is unusual. The obliteration of these traits by death may confuse the identification of dead bodies even in the absence of decomposition or mutilation.

From the viewpoint of identification, we can classify dead bodies as recognizable or unrecognizable. When a person dies under normal circumstances and is seen before decomposition has set in, there are usually ample means of identification in sight recognition which can be confirmed by fingerprints, if reference prints taken during life can be located. In the absence of such records, one must guard against erroneous identification. Such errors may be unintentional or they may be deliberate for fraudulent insurance claims, to escape punishment, or for some other reason.

Just as emotional reactions may adversely affect the reliability of visual recognition of living persons, they may also lead to unintentional errors in attempts to identify deceased persons. It is often difficult for a person asked to view a dead body to recognize a face which lacks the expressions that characterized it during life. The emotional reaction to the death of a beloved relative may influence one to reject the fact of the death and, therefore, the identification; another person may be so overwhelmed by grief that the assumed identification is accepted readily after only a cursory glance at the body.

Unintentional errors in identification reflect an ignorance of the implications of false identification. Persons who identify vagrants or "black sheep" of their families may not realize the need for accurate identification. The following case illustrates such an attitude.

Early in the morning of March 17, 1941, an unidentified man was found dead in a doorway of an office building in downtown Cleveland. Death had resulted from exposure. The following day a woman came to the coroner's office and described an uncle whom she had not seen for three years. She stated that her uncle had a crooked nose owing to an old fracture. The dead body exhibited evidence of an old nasal fracture, so she was permitted to view the body. She said she recognized the man to be her uncle, Michael C., age 73. She signed an affidavit to this effect and claimed the body for burial.

At the funeral home several people realized that the dead man was actually a younger brother of the purported deceased, Harry C.,

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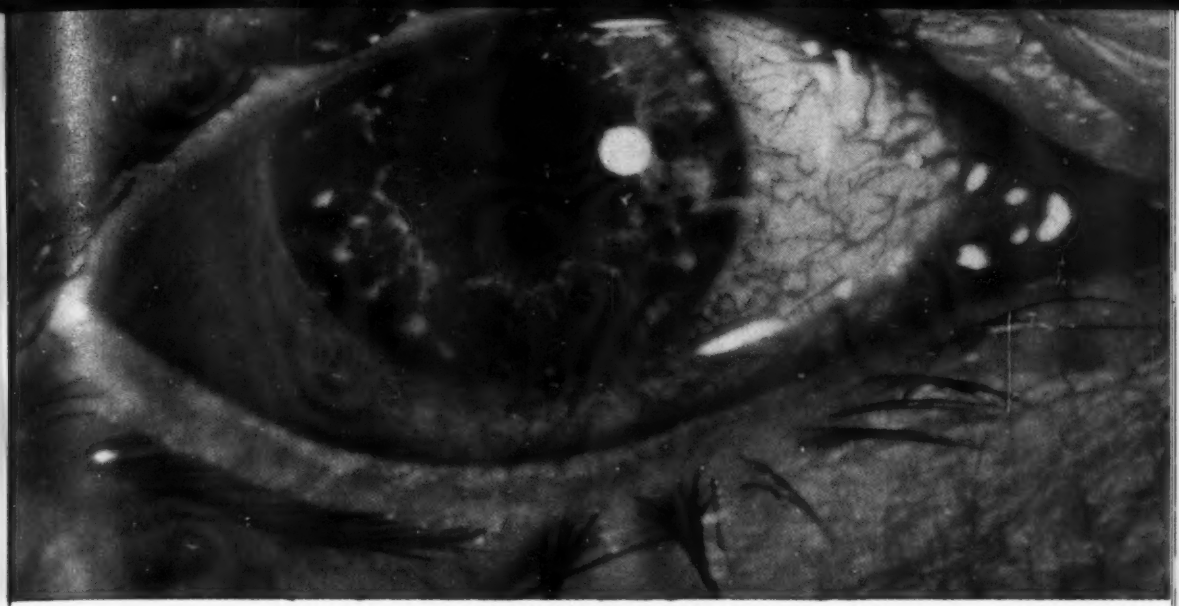

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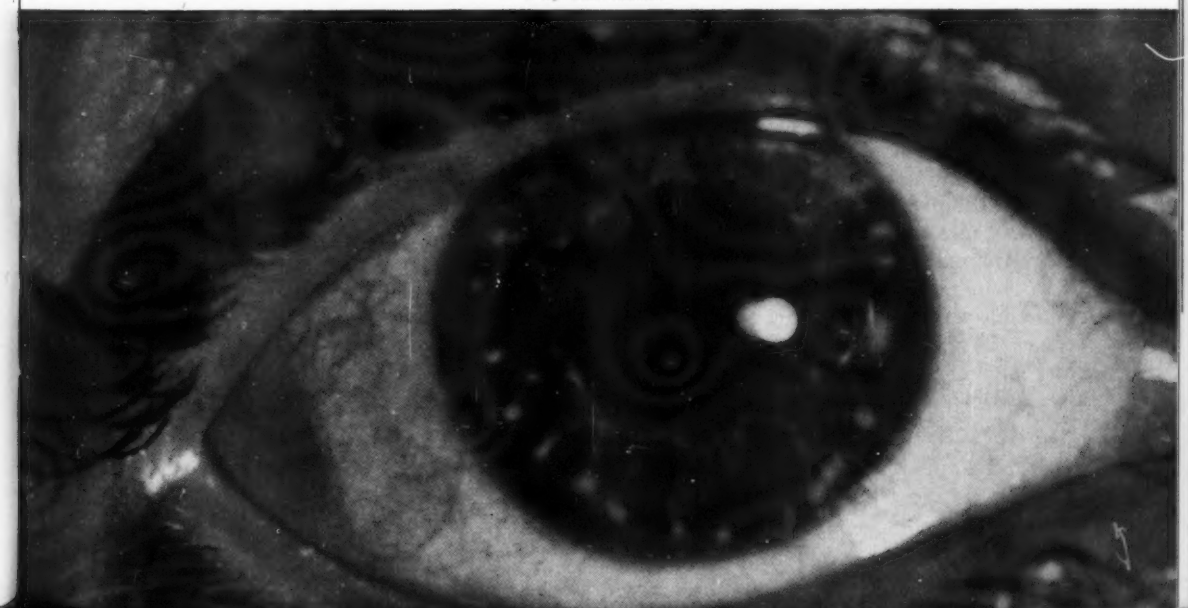

whom they had not seen for 40 years. Michael was living in a rooming house. His only income was his monthly check from the Division of Aid to Aged Persons. Other residents of the rooming house read his death notice in the paper and joked with him about it. The landlady phoned the funeral parlor and notified the family that Michael was alive and resided at her address. After the funeral, the niece who had made the identification visited the rooming house and admitted her error.

There was no attempt to correct the false identification until Michael's pension check failed to arrive at the usual time. When he complained to the Division of Aid, he was informed that his name had been taken off their list since legally he was dead and could not be reinstated until the error in identification was verified and corrected.

The body in question was exhumed. There was a striking resemblance in the facial features of the two brothers. Each had had a broken nose which had healed crookedly—one veering to the right and the other to the left. Fingerprints were obtained from both men, the living and the dead. Fortunately for our purposes, both men had been arrested and fingerprinted previously, so it was possible to establish conclusively the correct identifications. Michael was reinstated on the old-age pension rolls. Brother Harry had been 61 years old and therefore not eligible for such a pension.

This case illustrates the need for proper identification of a body at the time it is in the custody of the coroner or medical examiner, if at all possible. Whether or not identification is made, an accurate detailed description of the dead body must be recorded and filed. This precaution may resolve doubts and preclude disinterment of a body if the original description is questioned later.

When identification is not made before burial, all information available should be obtained from a thorough examination of the body, including roentgenologic and dental examinations and dissection for anatomic evidence. The record should include a detailed description of clothing and anything else found associated with the body. No minute detail should be neglected or considered insignificant. In one case of a badly decomposed body which was recovered from the river, it was noted in examining the clothing that the trousers had been mended with green embroidery floss. When the wife was asked for a description of the clothing her husband was wearing when he left home, she volunteered the information that the trousers were mended in this distinctive manner. Such minutiae frequently afford clues to identification.

Recognizable bodies may present challenging problems in identification when the usual clues are absent or when there is deliberate misrepresentation. The coroner or medical examiner must be circumspect about accepting any identification based merely on associated evidence such as hotel registrations or contents of billfolds, pockets and purses. He must consider the possible use of an assumed name and the fact that possession of billfolds, purses and miscellaneous papers does not necessarily denote rightful ownership.

Persons attempting suicide sometimes take measures which they hope will frustrate their identification. This was apparently the intent of a man who jumped from an office building. There were no labels in his clothing. His pockets contained no papers or personal property except spectacles which were in a case bearing an optometrist's name and address (figure 1a and b). The optometrist examined the spectacles and was able to produce the prescription card bearing the patient's name and address. Further investigation revealed that this individual was missing from his home, and friends who viewed the body were able to affirm the identification.

Another case of a suicide attempting to evade identification involved a woman who was found dead in a hotel near a bus station. She had registered as Mrs. R.W. of a nearby state. The cause of death was an overdose of barbiturates. The contents of her purse included a bus ticket indicating that she was en route from San Diego, California, to Utica, New York. Prescription envelopes in her purse bore the name under which she had registered at the hotel and the names of physicians in

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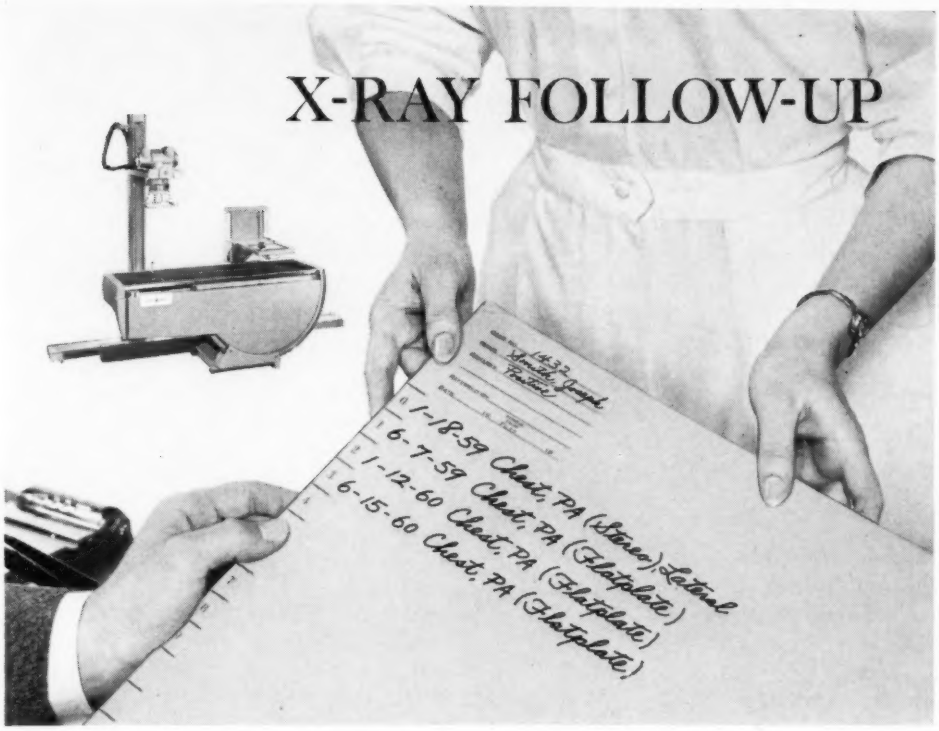

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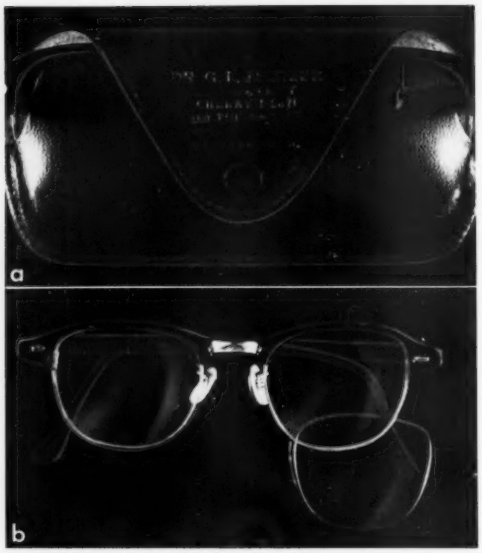

FIGURE 1. a and b. Optometrist's case and spectacles which led to identification of a suicide victim.

Utica. Telephone calls to these doctors failed to produce any clues to identification. The Utica police were informed of these facts and the description of the dead woman was read at roll call. One of the policemen thought that the description fitted a neighbor's sister who was separated from her husband and had gone to California. However, that woman's name was quite different (Mrs. L.C.).

It was established that the dead woman was the neighbor's sister. Her family in Utica had not known that she had left California and, therefore, no missing report had been filed.

When reference fingerprints taken during life are not available, it is necessary to turn to other individualizing features such as birthmarks, scars, tattoos and dental characteristics to confirm identification. The routine practice of noting such details in identifying recognizable bodies builds experience that guards against overlooking similar features which must be relied on to a greater extent in identifying unrecognizable bodies.

Bodies are reduced to an unrecognizable state by various types and stages of decomposition or putrefaction following prolonged exposure in air or submersion in water, by mutilation or by charring. One of the first questions to be resolved may be whether the remains are those of a human being or of an animal. The answer is found most readily in some cases by a study of x-ray plates. In other instances it may be more desirable to resort to dissection and immunologic procedures. Determination of sex, race, age and stature are other problems in identification of unrecognizable bodies. Solving these problems frequently requires the counsel of experts in comparative anatomy and anthropology.

Identification is often simplified when proper attention is given to clothing, contents of pockets, and material found associated with a body. In one case in our experience, an envelope found in the pocket of an unrecognizable body not only afforded a clue to identity but also delimited the time of death.

On July 10, 1956, a body was found in a vacant lot in Cleveland. Putrefaction had reduced the body to little more than a skeleton. Opinions based on external appearances estimated the time of death to range from three weeks to several months prior to discovery of the body. A routine search of the clothing yielded a letter bearing a postmark which proved that the letter had been sent by airmail from Puerto Rico on June 22, 1956, 18 days before the date the body was discovered (figure 2). The presumed date of delivery coincided with the date the addressee had last been seen alive as determined by investigation at his residence and place of employment. Identification was made by comparing the victim's teeth with the missing man's dental records. In addition, the clothing of the body was described and recognized by close friends.

In another case, a clue to identification was found in a money order receipt with a 1952 date. The receipt was found approximately 200 ft. from a naked mummified body which was discovered in March 1956. The name on the receipt expedited identification by fingerprints. Readable prints could be obtained from only two or three fingers of the body. The Cleveland police department had fingerprints on file for the person named on the receipt.

(Continued on page A-64)

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FIGURE 2. Postmark on envelope found on a body. Tracing the letter provided clue to later identification of body.

Comparison of the prints taken after death with those taken during life established the identity. It was found that this individual had been confined in penal institutions for various periods during his life. He had been released from prison about 10 months prior to March 1956. It was deduced from the condition of the body and the vegetation beneath the body that death had occurred soon after this release. A distinctive tattoo figure of a dragon was seen on the chest of this body. It was deplorable that none of the penal records mentioned this fact. Had it not been possible to obtain fingerprints, this body might not have been identified in spite of detailed studies to determine the race and age.

We have seen many cases in which identification would have been expedited if identification records made during life had included detailed descriptions of tattoos, marks, scars and notations concerning the type and extent of surgery when surgical scars are present.

One such case was of a drowning victim who was suspected to have been a crew member of a lake freighter which had sunk about nine months prior to recovery of the body. Fingerprints were obtained from two fingers after persistent efforts. Comparison of these prints with reference prints taken during life was not completely convincing proof of identity. However, the tattoo discernible on the upper arm and other features corresponded to the description of the missing person supplied by a relative. There was no mention of this tattoo on the official employment record. Certainly in hazardous occupations which might involve a disaster whereby elements of perceptible recognition of a body could be destroyed, detailed information of all anatomic clues to identity should be recorded in the medical history at the time of employment and kept up to date.

Mutilated and dismembered bodies present specific problems in identification. It must be determined that all parts recovered are human and belong to the same body. Whether mutilation occurred before or after death is also to be decided. As in the other cases cited here, a diligent study of associated materials may yield valuable clues to identity.

When recognizable features have been destroyed by fire, attention must be directed to anatomic evidence. However, the possibility of finding unburned fragments of clothing, jewelry and other personal property must not be ignored. X-rays of the body may reveal healed fractures and other conditions of bony structures which will provide clues to identity. X-rays will show the presence of metallic materials. During the East Ohio gas disaster in 1944 we were able to identify one portion of a charred body (figure 3a) because a truss was visualized on an x-ray plate (figure 3b). Without the x-ray study, it might never have been discovered in the charred torso.

The importance of examining the teeth of burned victims is well known.

Unusual dental evidence was found in a charred body recovered from the rubble of a

(Continued on page A-66)

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References: 1. Lineback, M.: The Eye, Ear, Nose and Throat Monthly *39*:342 (April) 1960. 2. Fuchs, A. M. and Maurer, M. L.: New York J. Med. *59*:3060 (August 15) 1959. 3. Kreindler, L. *et al.:* Antibiotic Med. and Clin. Therapy 6:28 (January) 1959. 4. Schiller, I. W. and Lowell, F. C.: New England J. Med. *261*:478 (September 3) 1959. 5. Edmonds, J. T.: The Laryngoscope *69*:1213 (September) 1959. 6. Horstman, H. A.: Am. Pract. & Digest Treat. *10*:96 (January) 1959.

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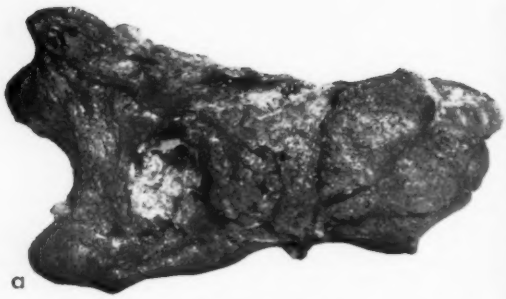

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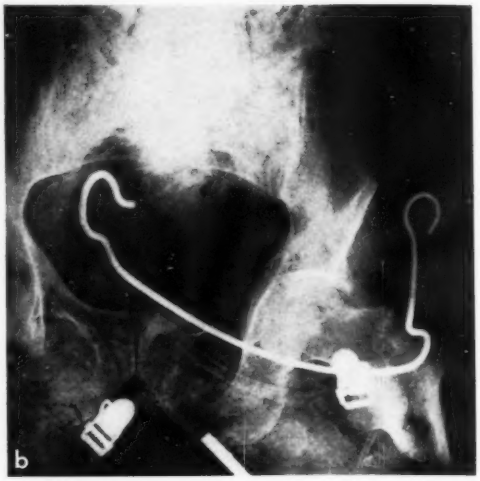

b

FIGURE 3. a. Portion of charred body which was apparently unidentifiable.

b. X-ray of pelvic section which revealed presence of a truss, leading to later identification of victim.

roller rink destroyed by a fire which occurred after the closing hour. Inquiry failed to reveal any clues to the body's identity, since it was presumed that no one was in the building at the time of the fire. A partially burned upper denture was found to bear a portion of a strip of paper embedded in the acrylic (figure 4). The letters "ghns" were discernible and suggested that the strip of paper may have borne the name of the individual. The presence of a navy ring on a charred finger led to notification of the proper authorities through whom identification was established as "Vaughns," a sailor who had been on leave and had not returned to base. The denture had been made while the man was in the service where it was customary to mark dentures with the wearer's name.

FIGURE 4. Portion of paper strip embedded in denture which aided identification of fire victim.

This incident has inspired a Cleveland dentist to advocate the universal adoption of a code for identification to be imprinted in each denture.

When mass disasters occur attention is focused on the importance of the methods of identification which are considered to be extraordinary. The few cases which I have selected from our experience and cited here demonstrate that attention to detail, persistence and patience frequently will overcome apparently insurmountable problems of identification of persons. It must be realized that although fingerprints are the ideal means of identification, they cannot be relied on as the only method, because comparable records may not be available. Therefore, it is advisable routinely to compile records of substantiating evidence from anatomic findings, individual characteristics and associated material which may be useful to establish the identity of a living or deceased person.

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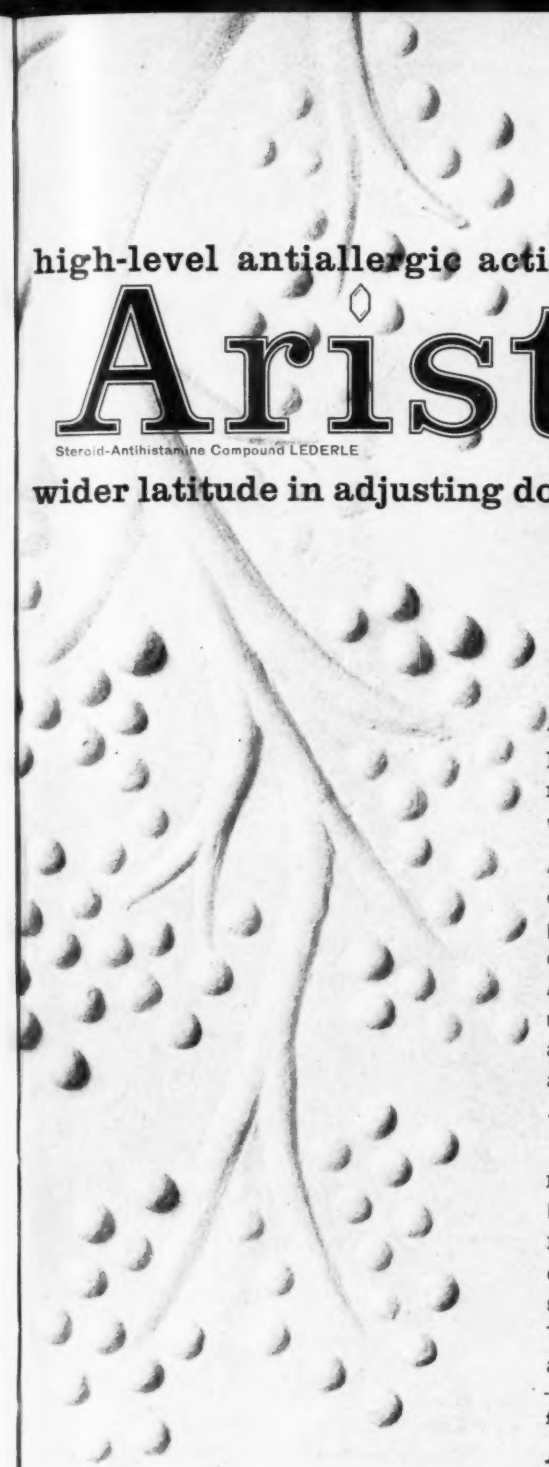

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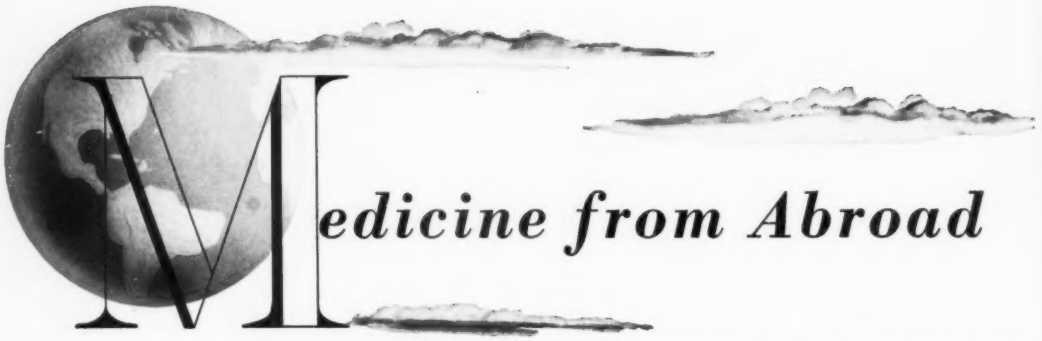

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SPAIN: MRS. EDITH BULSON
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For several weeks this spring, Dr. Malcolm McCannel, ophthalmologist of Minneapolis, Minnesota, served with the medical staff of the SS HOPE, anchored at Bima on the island of Sumbawa, about 800 miles from the Indonesian capital of Djakarta on the island of Java. Dr. McCannel wrote this report of the work of Project HOPE while still aboard the ship, and we are pleased to present his account of a truly humanitarian endeavor on the part of individual American physicians and other medical personnel.—The Editors.

INDONESIA—SS HOPE

Bima, Indonesia, 11 April, 1961

THE SS HOPE is part of a privately sponsored program to share the United States' modern medical knowledge and skills with newly developing countries. Project HOPE—Health Opportunities for People Everywhere—is a nonprofit, charitable organization which began over a year ago and was brought to fruition by the sailing of a converted hospital ship, SS Constellation, rechristened the SS HOPE I, from San Francisco last fall.

The ship has been in operation a little over seven months and has made island-hopping stops all along the equator in the Republic of Indonesia. Plans are being made for this ship or others like it to visit Vietnam, Pakistan, South America and Africa in the future.

The permanent medical staff of the SS HOPE includes 15 physicians, a dentist, and about 50 nurses and auxiliary personnel. Volunteer medical specialists join the ship on a rotating basis for tours of duty.

Two weeks ago the HOPE made an unscheduled stop at the city of Ende on the island of Flores. It was reported that a bad earthquake had hit the island, and we were asked to stop and give what aid we could. It turned out that there were few casualties but there was considerable damage to buildings.

At Bima, which is in a sheltered cove on the north side of the island of Sumbawa, there is one doctor for about 80,000 people. He is a very alert Indonesian of Chinese extraction named Dr. Tan Hong Djwan, who is a master diagnostician and with a small amount of equipment and ancillary help accomplishes miracles that we take for granted in the United States.

Approximately half an hour after the first launch from the ship arrived at the wharf, a polyclinic was set in operation. The patients are screened and sent to the various departments for

(Continued on page A-74)

Put your low-back patient back on the payroll

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evaluation. For the most part, only problem cases are handled on the ship because of lack of time and of bed space. Patients seen one day are scheduled for operation the following day. The operating rooms are ably managed by Mavis O. Pate, Tyler, Texas, and she keeps her three operating rooms humming from 7 A.M. until late in the afternoon. In the last two weeks, Dr. Robert Pulliam, Longview, Washington, has done over 25 operations for repair of harelip. There is a comparable amount of pathologic conditions requiring general surgery and eye and chest care. Tuberculosis is very prevalent on Sumbawa, and at present the ship is in dire need of an orthopedic consultant.

There is nothing hit-and-miss about the record-keeping and paper work. Occasionally, a disgruntled surgeon may wish for the retinue of interns and residents he would have at home as he completes the endless charting and surgical reports to make this a worthwhile project.

A great change has been seen in the Indonesian personnel since they first joined the ship in Djakarta and Surabaja last fall. Local nurses now pick up, play with and fondle pediatric patients in the same way as their American counterparts, which they did not do at first. They also have expressed amazement at the concentrated team effort put forth when a problem case goes sour and requires a lot of extra work.

This morning a 7 lb. tumor was removed from the left parotid area of a woman who had had it for over 21 years. The tumors, hernias and healed fractures look like the examples in medical books published at the turn of the century.

The trip to and from the hospital and polyclinic is like a tourist's dream. There are rice paddies with water buffalo and occasionally a crocodile, and colorful thatched-roof houses on stilts, which provide a playroom for the children during the hot days and a cooler place to sleep in at night. Goats, monkeys and little ponies are seen everywhere. A favorite pet is a parrotlike bird with an enormous bill and an odd cry. Many of the children fly kites. On each island, the people seem to have their own special type of sailing craft with a particular design of sail and outriggers. Indonesians are small, reserved, pleasant and appreciative people. They have the typical Far Eastern solicitude for their children, and we find that both children and adults take one-half to one-third of the usual pain-killing remedies needed in the United States.

Everyone is used to waiting in the Far East and appointment schedules often mean very little. At first this was a most frustrating source of exasperation, but countermeasures have been resorted to and now even the Indonesians forego some siesta time if a clinic is scheduled.

The mechanics of running this hospital ship is a huge task. In port we use almost 150 tons of fresh water per day, and the laundry handles as much dirty linen as a small city. Al Adams, of San Francisco, has a "mechanical cow" in No. 5 hold deep amidships. By ingenious use of milk powders, chipped ice, colorings, anhydrous fats and other additives, it is pretty hard to tell it from the real thing. The chocolate milk or "susu" is the most popular item with the Indonesian patients.

Since this is a hospital training ship, teaching of local personnel accompanies treatment of patients. There are classroom lectures, discussions, movies, film strips and demonstrations going on every day.

Millions of people in Indonesia are caught in a vicious circle. Poverty, malnutrition and disease are very common. Unhealthy people find it hard to produce, and this new Republic of Indonesia does indeed need healthy people to produce.

Project HOPE includes land-based operations of mobile jeep teams of doctors and technicians who go inland to share knowledge and help the Indonesians to help themselves.

The SS HOPE at present is the major activity of the People-to-People Health Foundation, Inc. This nonprofit, nongovernmental organization is sponsored by industry, unions and private donations. American President Lines operates the SS HOPE at cost, and the American petroleum industry furnishes all fuel. Pharmaceutical firms generously donated our drugs, surgical instruments and many of our supplies. Although many of our foodstuffs are utilized by the ship's personnel, a generous amount is left on the docks at each port—powdered milk, soap, rice, flour and pharmaceuticals.

The people on the HOPE feel there is a great wellspring of good will for the United States here in Indonesia. The HOPE has no ax to grind and is purely an expression of the American people who want to help those who are less fortunate than themselves. It is a mere drop, of course, but with every dollar and ounce of energy used, it is hoped that we are making friends for America in Far Eastern Asia.

(Continued on page A-77)

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DARICON is oxyphencyclimine hydrochloride, a long-acting, highly effective anticholinergic. DARICON provides 24-hour relief from the pain and discomfort associated with g.i. disturbances, usually on just b.i.d. dosage.

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Side Effects and Precautions: Dryness of the mouth is the most common peripheral effect. Blurring of vision, constipation, and urinary hesitancy or retention occur infrequently. These effects may decrease or disappear as therapy continues, or can be minimized by adjustment of dosage. Care should be exercised in using DARICON in patients with prostatic hypertrophy, in whom urinary retention may occur. The use of DARICON as well as other anticholinergics in patients with an associated glaucoma is not recommended except with ophthalmological approval and supervision.

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AUSTRALIA

Pulmonary hydatid disease—In the *Medical Journal of Australia*, Drs. R. W. Haber, Maurice Joseph and A. F. Grant, Royal Prince Alfred Hospital, Sydney, have reported on a series of 65 patients who were hospitalized between June 1945 and June 1960 for hydatid disease of the thorax.

Although hydatid disease has a world-wide distribution, the greatest incidence is in Australasia and South America. In a survey covering the years 1957 and 1958, Gemmell found that 32.2 per cent of the dogs in the southern tablelands of Australia were infested with *Echinococcus granulosus* and the incidence of infestation was as great among the pet dogs kept on homesteads as among working sheep dogs. The incidence of hydatid disease in humans is distributed almost equally in all age groups, with a peak in persons whose ages range from 11 to 30 years.

Of the 65 patients in this series, the hydatid cysts were confined to the lungs in 47; in 11 the liver was also involved. In the remainder of the patients, other organs were affected. Eighty-one per cent had pulmonary symptoms (most frequently, a pneumonic episode) when first seen.

Casoni's test gave positive results in 47 per cent of the patients in whom it was carried out. The result of the hydatid complement-fixation test was positive in 55 per cent of those in whom it was performed; however, a positive result did not necessarily prove that the rounded shadow in the lung was a hydatid cyst. In nine patients, microscopic examination of the sputum showed some hydatid elements.

Significant eosinophilia was present in 20 per cent of these patients. Diagnostic bronchoscopy was performed in 11 patients; in nine of these, congestion of the bronchial mucosa was the only abnormality observed. Bronchograms were made in only four instances; in one the dye was shown entering a cyst, and in two displacement of bronchi was observed. In 72.5 per cent of the patients, abnormal physical signs in the respiratory system were recorded, but these were not diagnostic.

The authors stated that if a pleural effusion occurs, the fluid should be examined for hydatid

(Continued on page A-78)

elements and for eosinophilia. They believe that every hydatid cyst should be surgically removed as soon as diagnosed, since the danger of thoracotomy is less than that of spontaneous rupture. Excision of the cyst with obliteration of the cavity is the standard procedure.

Hydatid disease could be easily prevented by simple measures which break the life cycle of the parasite and prevent human infestation. However, in the last 30 years there has been no decrease in the incidence of infestation in sheep or dogs and no decline in the number of patients with this disease treated at the Royal Prince Alfred Hospital.

AUSTRIA

Therapeutic pseudopregnancy—In a lecture to the Austrian Society for Gynecology and Obstetrics, Dr. W. Hofhansl stated that a pseudopregnancy (false pregnancy) can be produced by administering luteotropic chorionic gonadotropin or a combination of progesterone and estrogens. The procedure affects both the uterus and the endocrine system. Patients must be selected carefully for such therapy. Dr. Hofhansl believes it is justifiable only in cases of primary sterility and of amenorrhea, and that it should be used only as a last resort after all other treatment has proved ineffective.

Dr. Hofhansl reported on employing pseudopregnancy in 44 patients over a period of three and one-half years. Production of the pseudopregnancy required about seven weeks. During this period, depot hormones were given in increasing doses until a total of 2,880 mg. depot PROLUTON® and 70 to 80 mg. depot PROGYNON® had been given. Although the episodes of bleeding after the pseudopregnancy were irregular, they had a certain concordance. The procedure also had a beneficial effect on secondary symptoms such as hypoplasia of the uterus and dysmenorrhea. In many cases, Primosiston was given after the pseudopregnancy in order to control the resultant hemorrhage and to obtain early regularity of menstrual periods.

Nine of 26 women with primary sterility became pregnant within five to eight months after the pseudopregnancy. Of 36 patients who had had recurrent secondary amenorrhea of at least five months' duration, 14 were cured by the procedure, seven received no benefit, and 15 are still being treated. The procedure caused an average enlargement of 2 cm. in the size of the uterus in 42 women who had uterine hypoplasia. This enlargement can be expected to be permanent. Fourteen of 18 women with dysmenorrhea obtained relief for from five to seven menstrual periods following the pseudopregnancy; however, the dysmenorrhea then gradually returned. In almost all patients, the endometrium underwent decidual transformation.

Dr. E. Heissenberger reported on the use of pseudopregnancy in a 17½ year old girl who had hypoplasia of the uterus and oligomenorrhea. Although the uterus did not increase substantially in size, the secondary sex characters became more marked. Toward the end of treatment, pigmentation similar to chloasma uterinum appeared on the patient's face.

To illustrate the dangers of pseudopregnancy, Dr. E. Gitsch told of a 25 year old woman who was treated by another physician for a hypoplastic uterus. The uterus before treatment measured 5½ cm. in length, and the patient had a biphasic menstrual cycle. A pseudopregnancy was induced according to Kaiser's method. Marked bleeding with desquamation occurred 14 days after the last injection and lasted eight days. Amenorrhea then developed, and the patient's temperature became subnormal. This condition continued for four months, at which time the patient was seen by Dr. Gitsch. The uterus then measured 6 cm. in length. Intensive use of the follicle hormone for several weeks produced continued cessation of the gonadotropic cycle in this patient.

BRAZIL

Tuberculosis and ventricular aneurysm—Although tuberculosis is not usually cited as a cause of ventricular aneurysm, Drs. J. F. Carneiro and N. B. Reis have reported nine cases of an aneurysm of the left ventricle in which tuberculosis was the indisputable cause and six cases in which it was a likely cause. Caseous

(Continued on page A-80)

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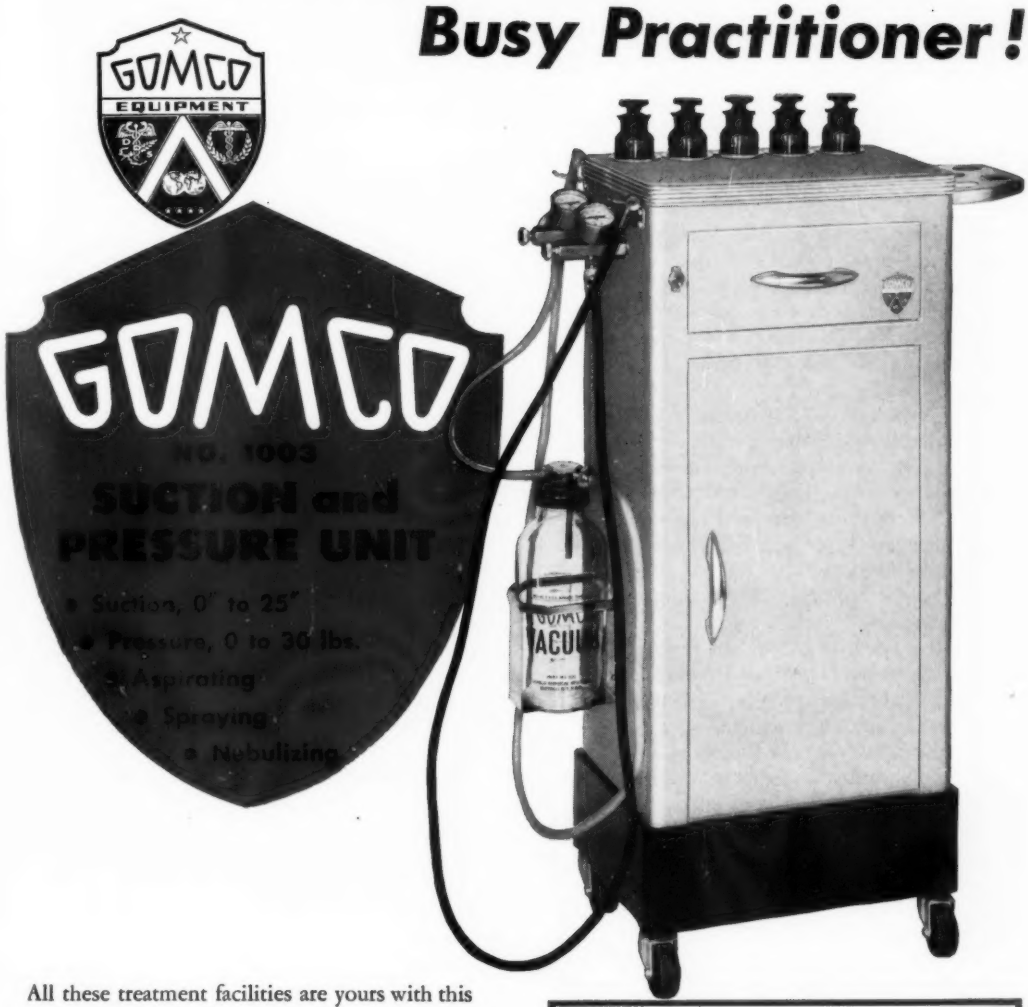

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lymph nodes were found in the mediastinum in all patients concerned.

Visceral tuberculosis and tuberculosis of the lymphatic glands frequently are found at postmortem examination of patients with a ventricular aneurysm of obscure cause in whom there is no evidence of a coronary occlusion. A common site of such aneurysms is the region of the mitroaortic ring of the posterolateral surface of the ventricle. The diagnosis of aneurysms caused by tuberculosis usually has been made post mortem, but Drs. Carneiro and Reis have reported on three cases of calcified ventricular aneurysms in which the clinical findings, histories and follow-up observations showed that coronary sclerosis was not present and that tuberculosis was the etiologic factor.

Aneurysms of the left ventricle may rupture and cause death or may persist and eventually show a ring of calcification. These rings often have been wrongly interpreted as echinococcus cysts of the myocardium, and cases of calcified ventricular aneurysm have been incorrectly diagnosed as hydatidosis.

This report appeared in the *Anais da Faculdade de medicina de Pôrto Alegre.*

Electroshock therapy—In the *Revista paulista de medicina,* Drs. H. B. Diniz and A. Benini have reported on a technic for administering electroshock therapy to outpatients.

Because many patients fear shock and because good results cannot be expected until a complete series of treatments has been given, electroshock therapy has hitherto been administered only to hospitalized patients. Drs. Diniz and Benini have made possible the administration of electroshock therapy to outpatients by giving thiobarbiturate to induce a preshock sleep. Only 0.1 per cent of outpatients treated over a period of five years experienced either fear of shock or postcrisis psychomotor agitation. Most of these patients completed treatment; in 21.8 per cent treatment was abandoned for various reasons.

Electroshock therapy was administered without complication to 47 patients with hypertension, 44 with neurologic disorders, five with cardiovascular disease, and two with disease of the lungs. Auricular fibrillation and cerebral embolism developed in one patient who had aortic insufficiency. The administration of electroshock therapy or thiobarbiturate or both was responsible for vertebral fractures in three patients, development of jaundice in one, and spontaneous convulsion in one; in each instance treatment was interrupted. Studies of blood pressure and pulse and electrocardiographic studies showed no alterations which would justify interrupting treatment in the remaining patients. No deaths resulted from the administration of electroshock therapy to this series of outpatients.

ENGLAND

Chronic pyelonephritis—It is doubtful if the results of treating established chronic pyelonephritis have appreciably improved since the introduction of antibiotics and chemotherapeutic drugs. When advanced renal scarring is present, it is obvious that antibacterial therapy cannot reverse the lesions. For that matter, it is uncertain if even successful control of infection has much influence on the progression of chronic pyelonephritis when it has reached a certain stage.

In a symposium on genitourinary disorders in the *Practitioner,* Dr. A. R. Harrison, St. Peter's Hospital, London, has stated that when bacteriologic studies reveal that active infection is present an attempt must be made to eradicate or, at least, control it. In most cases it is possible to sterilize the urine by the use of appropriate antibiotic or chemotherapeutic drugs, but this does not represent a cure.

Numerous studies show that relapses are common, particularly when chronic pyelonephritis is a complication of other lesions of the urinary tract. Relapses may be due to the same organism, to the emergence of resistant strains of that organism, or to entirely different bacteria. We do not know whether these relapses represent a true reinfection of the kidney from some reservoir such as the colon or whether they result from failure to eradicate organisms from the renal tissue. There is little doubt that some relapses are due either to the use of inadequate doses of antibacterial drugs or to insufficiently prolonged treatment. If chronic pyelonephritis is believed to be an interstitial infection of the renal tissue, then any antibiotic or sulfonamide must be given in amounts appropriate for treatment of any tissue infection. It is easy to sterilize the urine and presumably to eradicate surface infection of

(Continued on page A-82)

Three of these women have vaginitis (trichomonal, monilial or mixed). Only comprehensive therapy can reach all three.

For every 2 cases of vaginitis caused by Trichomonas vaginalis alone, there is usually 1 case caused by Candida (Monilia) albicans, Haemophilus vaginalis, or mixed infection involving several pathogens.[1-3]

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1. Coolidge, C. W.; Glisson, C. S., Jr., and Smith, A. A.: J. M. A. Georgia 48:167 (Apr.) 1959. 2. Ensey, J. E.: Am. J. Obst. & Gynec. 77:155 (Jan.) 1959. 3. Frech, H. C., and Lanier, L. R., Jr.: J. M. A. Georgia 47:498 (Oct.) 1958.

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the urinary tract with quite small doses of those antibacterial drugs which are excreted in the urine in high concentration. This, however, is not the aim of treatment. Nevertheless, long-term, so-called suppressive chemotherapy may be of value in cases in which the kidney is constantly being reinfected by the urine.

Most cases of pyelonephritis are associated with other disorders of the urinary tract. Not all of these can be corrected by surgery, nor is an operation for the relief of obstruction necessarily followed by the disappearance of infection. Nevertheless, all patients with persistent or recurrent infection should undergo a thorough urologic examination, for the difficulties of eradicating infection in the continued presence of other renal or urinary tract lesions are almost insurmountable.

Erythema nodosum—The disease erythema nodosum was named and described by Dr. Robert Willan in 1808. We are still undecided about its pathogenesis, confused on the relative frequency of its different causes, and have no better treatment than the Peruvian bark advocated by Willan.

In the *British Medical Journal*, Dr. Geraint James, Royal Northern Hospital, London, has published a careful study of 170 patients with erythema nodosum observed between 1950 and 1959. He stated that the disease has a seasonal incidence, occurring most often in the spring. It is three times more common in women, particularly affecting those of childbearing age. Polyarthralgia commonly precedes or accompanies it.

Of the 170 patients studied by Dr. James, 126 had evidence of sarcoidosis, and 21 had various infections; in the remaining 23, the cause was unknown. Evidence delineating the sarcoidosis group included bilateral hilar lymphadenopathy, positive results of Nickerson-Kveim tests, and other histologic evidence of sarcoid tissue. Streptococcal infection was suggested by raised and changing serum antistreptolysin titers. Tuberculosis, pneumonia, a dental abscess, and acute colitis were uncommon concomitants. Since erythema nodosum itself affords no clue to the cause, the most informative investigations for distinguishing contributory factors include a chest x-ray, the Nickerson-Kveim test, the antistreptolysin titer and the Mantoux test.

Irrespective of the causes observed in this series, the prognosis of erythema nodosum and its associated clinical and radiologic abnormalities is excellent. Since spontaneous recovery is the rule, there is rarely any indication for special treatment.

ISRAEL

Amebic granuloma—L. Szymanski and Z. Teva, Kaplan Hospital, Rehovot, have reported on 22 cases of amebic granuloma (ameboma) of the colon. This unusual complication of amebiasis frequently causes diagnostic problems. An acute condition of the abdomen was the initial diagnosis in nine patients in this series, and six patients underwent operation for suspected acute appendicitis. In several patients, barium enema studies aroused suspicion of carcinoma of the colon.

The most common presenting symptom was severe abdominal pain, and tenderness in the right iliac fossa was noted frequently. Only eight patients had diarrhea; amebas were found in the stools of 10 patients. Three patients had a history of previous amebiasis.

Administration of emetine is the treatment of choice for amebic granuloma. Surgery should be performed only as an emergency measure for certain complications, as it may have grave and sometimes fatal results.

Familial Mediterranean fever—In a preliminary report on immunologic findings in familial Mediterranean fever, A. Shachter-Many, M. Pras, E. Sohar, H. Heller, E. Eilan and J. Kedar have presented the results of a study in which rabbits were immunized with a substance from the lardaceous spleen of a patient with familial Mediterranean fever. The antiserum obtained was tested by the agar-gel diffusion technic against the serums of patients with this disease. A specific, additional band was seen in 50 of 51 cases, whereas positive findings were noted in only four of 153 control subjects, two of whom were suspected of having familial Mediterranean fever. The diagnostic value of this test is apparent; however, it still is not clear whether the result is a direct expression of the genetic biochemical deviation or whether it is a response to the clinical manifestations of the disease.

These reports appeared in *Harefuah*.

THE SCHNEIDER FOUNDATION EYE PRESENTATION

Use of Newer Drugs in Relation to Ophthalmology

IRVING H. LEOPOLD*

University of Pennsylvania Graduate School of Medicine, Philadelphia

The main therapeutic approach to toxoplasmosis is a combination of pyrimethamine and sulfonamides.

Wilson's disease (hepatolenticular degeneration) responds to a copper-poor diet and agents that remove copper from the tissues.

Two new anticholinesterases used to treat glaucoma are Phospholine iodide and demecarium bromide. Compounds to reverse the action of anticholinesterases also are being studied, e.g., 2-pyridine aldoxime methiodide.

Neostigmine administered locally may help control the ocular manifestations of myasthenia gravis and aid in diagnosis.

Steroids given for systemic diseases may produce unusual ocular side effects, and some drugs that may be instilled in the eye may produce serious systemic disorders. Tranquilizers also have produced some unusual complications.

Toxoplasmosis

IRVING H. LEOPOLD

In 1922 a Czechoslovak ophthalmologist, Janku, described congenital ocular toxoplasmosis, and in 1927 a Brazilian ophthalmologist, Torres, added a second case to the literature. It remained for Wolfe, Cowan and Paige in 1939 to demonstrate a *Toxoplasma* organism in the tissues of an infant with the syndrome previously described as congenital toxoplasmosis. This syndrome has become well known, and pediatricians, neurologists, obstetricians, gynecologists and pathologists as well as ophthalmologists have contributed to knowledge of the entity. It is apparent from serologic studies, cultures of blood and histologic studies of tissue that toxoplasmosis produces chorioretinitis, cerebral calcification and neurologic symptoms and also that it resembles erythroblastosis fetalis, a similarity described by Eichenwald in 1956. In addition, acute infections with *Toxoplasma* organisms can occur in adults, in whom they often take the form of lymphadenopathy.

*Professor of Ophthalmology and Chairman of the Department of Ophthalmology, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pennsylvania.

Presented before the forty-fifth annual Assembly of the Interstate Postgraduate Medical Association at Pittsburgh.

TABLE 1

CONDITIONS IN WHICH SERUM TESTING FOR TOXOPLASMOSIS IS INDICATED

Fever of unknown origin
Lymphadenopathy
Infectious mononucleosis
(Paul-Bunnell test negative)
Relative lymphocytosis
Encephalitis
Serous meningitis
Exanthema (resembling typhus)
Chorioretinitis
Myocarditis

TABLE 2

REGIMEN FOR TREATMENT OF WILSON'S DISEASE (HEPATOLENTICULAR DEGENERATION)

To minimize absorption of copper:
1. Copper-poor diet
2. Potassium sulfide, 20 mg. with each meal
To promote urinary excretion of copper:
1. Penicillamine, 1 to 4 gm. daily, in divided doses (empty stomach)

Toxoplasmosis may be diagnosed by culturing the organism from the blood or tissue. Serologic tests include the Sabin-Feldman test, Jacob's hemagglutination test, the O'Connor precipitation test, and a complement-fixation test. Frenkel introduced a skin test.

It is advisable to suspect toxoplasmosis when a patient presents any of the signs listed in table 1. A fever of unknown origin, lymphadenopathy (particularly when you suspect infectious mononucleosis and the Paul-Bunnell test yields negative results), encephalitis, unexplained exanthema (particularly with chorioretinitis), or myocarditis for which a definite cause cannot be established should be an indication for Sabin-Feldman dye tests or Jacob's hemagglutination tests as well as skin tests.

Therapy for toxoplasmosis is available and consists largely of the use of sulfonamides, which have been shown by Eyles and Coleman, Kass and Finland, Warren and Sabin, and other investigators to be effective in experimental animals. At present, although the sulfonamides and some of the antibiotics may be effective against toxoplasmosis, the most commonly employed combination of drugs is DARAPRIM® (pyrimethamine) and sulfonamides. Initially a "priming" dose of 100 to 150 mg. of Daraprim is given; a dose of 100 mg. is given the second day. Maintenance doses of 75 or 50 mg. are continued for several weeks. Because Daraprim is a toxic agent that interferes with metabolism of folic acid, the blood picture must be watched closely. If a disturbance in the blood picture occurs, folinic acid (LEUCOVORIN®) can be administered or Daraprim can be discontinued. Transfusions may be advisable if the disturbance is severe.

Unfortunately, Daraprim and sulfonamides do not clear up all toxoplasmatic infections, for some are not due to active multiplication and growth of organisms but rather represent exacerbations of a pre-existing infection that has become encysted and is leaking toxic material into the eye or other tissue in which it resides. So we are searching for better antibiotics and better chemotherapeutic substances effective in *Toxoplasma* infections as well as for a means of controlling hypersensitivity reactions to toxoplasmin. Spiramycin, one of the newer antibiotics, seems to have some efficacy against toxoplasmosis, but this has not been proved.

Wilson's Disease (Hepatolenticular Degeneration)

Another entity seen in ophthalmologic practice (albeit rarely) for which therapy has been poor in the past is Wilson's disease or hepatolenticular degeneration. You are familiar with the neurologic signs of this disease and with the fact that a colored ring (Kayser-Fleischer ring) appears on the back of the cornea. For years it was thought that this represented a deposition of certain metals, and most recently it has been considered a deposition of copper. Perhaps there is some fault in the metabolism of copper or in its transport. There may be an inadequacy of ceruloplasmin to carry the copper and keep it from being deposited in the tissues.

A therapeutic regimen for Wilson's disease (table 2) should include reduction of dietary copper and administration of substances such as potassium sulfide to remove copper from

the gastrointestinal tract. To promote removal of copper from the tissues, penicillamine may be given orally (1 to 4 gm. daily). BAL (dimercaprol) also may be useful for this purpose but the intramuscular injections must be given daily, and hence preference is given to penicillamine, which can be administered orally. Some of the cation exchange resins also help remove copper from the tissues. With this type of regimen it has been possible to show a clearance of the Kayser-Fleischer ring, demonstrating the loss of copper from this tissue. Patients who have been followed for about five years have had definite improvement of neurologic symptoms as well as of the eye findings.

Complications of Tranquilizers

Tranquilizers are used in ophthalmology to enhance analgesia, to allay anxiety, and as preoperative and postoperative medication. Many complications of their use have been encountered. In addition to the familiar ones, a rather peculiar group of extrapyramidal symptoms have been noted in association with the phenothiazine derivatives such as COMPAZINE® and TRILAFON® (figure 1). These symptoms usually appear after the drug has been given for a number of days, but the young lad shown in figure 1 received only a single dose of Compazine. We have seen the same picture in an adult (30 years) following administration of Trilafon. It must, of course, be differentiated from other disturbances that might involve the central nervous system. The boy illustrated in figure 1 had an oculogyric crisis, rhythmic motions of the hands, and a cogwheel type of rigidity. The symptoms clear when the drug is withdrawn; barbiturates sometimes can be helpful in the acute phase.

Side Effects of Steroids

The steroids produce many side effects that are familiar to all physicians. However, in ophthalmology we see certain complications of steroid therapy that are less well known. Local use of steroids can aggravate dendritic keratitis, an inflammation of the cornea due to invasion of the virus of herpes simplex,

FIGURE 1. Oculogyric crisis, rhythmic motions of the hands, and cogwheel type of rigidity following administration of a single dose of Compazine.

to the point of perforation and loss of visual function. One must guard against the use of steroids in herpetic keratitis and also against the indiscriminate application of steroids in the cul-de-sac in patients who do not have this disease, for herpetic keratitis can develop very readily in an eye overtreated with steroids.

Prolonged use of prednisolone ointment in the eye may be followed by a punctate staining of the cornea and little breaks in the corneal epithelium which disappear when the use of prednisolone is stopped. One can readily understand how these epithelial breaks can destroy the barrier to viral and fungous infections of the cornea.

Another complication of long-continued use of steroids has been described by Von Sallman and Bunim in patients with rheumatoid arthritis who have taken steroids for months or years. It is a subcapsular opacity of the lens,

TABLE 3

LOCAL OCULAR DRUGS INDUCING IATROGENIC SYSTEMIC DISORDERS

Adrenergic agents (phenylephrine, epinephrine)
Cholinergic blocking agents (atropine, scopolamine)
Antibiotics (penicillin)
Anesthetics (cocaine)
Anticholinesterases (BC 48 or HUMORSOL®; PHOSPHOLINE® or 217-MI)

said to be visible with an ophthalmoscope. This change in the lens does not produce visual loss in the early stage. The patients have not been followed for a long enough period for it to be known whether or not the opacity of the lens will progress to visual loss, but certainly if you find that one of your patients who has been taking steroids for a long period has this change you will have to re-evaluate the necessity for using steroids. It is not an absolute contraindication to steroid therapy, for it does not necessarily impair visual acuity and it has not progressed when steroids have been discontinued.

Elevation of intracranial pressure has been observed in asthmatic children treated with triamcinolone. Two patients who had been given prednisolone for one and for two and one-half years, respectively, were switched to triamcinolone and in a few months exhibited retinal hemorrhage and papilledema.

Serious Systemic Disorders Produced by Locally Administered Ophthalmic Drugs

You are familiar with the necessity for alertness in the use of anticholinergic drugs in treatment of peptic ulcers. Such a drug can precipitate a rise in intraocular pressure, particularly in patients who have narrow angles in the anterior chambers and are predisposed to angle-closure glaucoma. You are also aware that antihypertensive drugs that reduce blood pressure precipitously may produce visual loss by closure of the central retinal arteries, leading to inadequate blood supply to the retina. Gordon Bruce and other writers have reported cases of this sort, particularly when ganglionic blocking agents have been used. Some drugs that may be instilled in the eye, on the other hand, may produce serious systemic disorders (table 3). For example, cerebral accidents (subarachnoid hemorrhage, hemiplegia) have occurred following subconjunctival injection of NEO-SYNEPHRINE® (phenylephrine) in an attempt to break up synechiae and dilate the pupil. You are familiar with the flushing and other systemic anticholinergic effects in children in whom atropine is applied topically for refractive purposes. Patients who instill scopolamine in the eye once or twice a day after an intraocular surgical procedure may have bizarre psychiatric symptoms of confusion, disorientation and indecisiveness and may be referred to a psychiatrist unless care is taken in eliciting a history of use of the preparation.

Antibiotics used locally can produce sensitivity that may endanger the patient when the drugs are later given systemically. Cocaine no longer is used for ophthalmic purposes because of idiosyncrasies to it; this drug can bring about mental confusion, headaches and collapse, and it also produces significant corneal epithelial disturbance.

Anticholinesterases in Treatment of Glaucoma

Recently, powerful anticholinesterases have been used for treatment of glaucoma. Within the past 10 years DFP (diisopropyl fluorophosphate) has become an important drug in the control of this disease. It is unstable in water and requires an anhydrous peanut oil vehicle. Within the past three years two new drugs have been introduced for the control of glaucoma. PHOSPHOLINE® iodide (also known as echothiophate) has an advantage over DFP in that it is stable in water and thus does not require an anhydrous vehicle. It is a long-acting anticholinesterase and is useful in glaucoma. Demecarium bromide (BC 48 or HUMORSOL® is also a long-acting anticholinesterase, but its structure is different from that of Phospholine iodide.

Because repeated instillations of these drugs into the cul-de-sac must be made over months and years to control intraocular pressure and prevent visual loss, it is possible that enough of the agents will be absorbed into the system to produce effects due to suppression of cholin-

FIGURE 2. Positive response to Prostigmine applied locally as a test for myasthenia gravis. After instillation of Prostigmine in right eye, ptosis improved.

esterase in the red blood cells and in the plasma. Measurements of the values for cholinesterase in normal and glaucomatous patients and in patients who received DFP (0.25 and 0.05 per cent solutions) for several months have demonstrated that the DFP did not depress the red cell cholinesterase appreciably. When eserine is used locally, there may be significant depression of the cholinesterase in an occasional patient. With demecarium bromide (Humorsol), significant depression of the cholinesterase was observed in many patients after three months of therapy. A large number of the patients who received Phospholine iodide (echothiophate) had depressed cholinesterase values.

These findings do not mean necessarily that all the patients whose cholinesterase values are depressed will have symptoms resulting therefrom, but some of them will. A variety of symptoms are noted, involving the bronchial tree and gastrointestinal tract, all due to overactivity of the parasympathomimetic system consequent to inhibition of the enzyme cholinesterase, which allows acetylcholine to act for a longer period of time and to a greater extent. These are simply the symptoms one would see with overstimulation of the parasympathomimetic system. There have been two cases reported in which patients who had been taking anticholinesterases for glaucoma underwent laparotomy on the basis of symptoms that pointed in this direction. Occasional patients have become mentally confused when they have taken these drugs for a prolonged period.

It is important to realize that although these agents all are labeled anticholinesterases they do not all act in the same way. PROSTIGMINE®, for example, has a short, reversible union with the enzyme. In myasthenia, Prostigmine is more dramatically effective than eserine or DFP. Prostigmine causes depression of the central nervous system; eserine or DFP causes excitation. The latter effect may be related to the lipid solubility. Prior instillation of Prostigmine or eserine blocks the action of DFP, whereas if DFP is employed first, followed by eserine or Prostigmine, the action is enhanced. Duration of action and the kind of cholinesterase inhibited also are different. Demecarium bromide (BC 48) inhibits specific cholinesterase; DFP and Phospholine iodide inhibit both specific and nonspecific cholinesterase, mostly the latter. All increase the facility of outflow, which is the main mechanism by which lower intraocular pressure is effected.

Compounds are being investigated that can reverse the action of the anticholinesterases. These are the oximes. Most promising is 2-PAM or 2-pyridine aldoxime methiodide. This compound, given by subconjunctival injection, can overcome the cholinesterase-inhibiting effect of some of these strong agents such as Phospholine. Protopam iodide or protopam chloride given subconjunctivally can definite-

TABLE 4

SOME OCULAR CONDITIONS FOR WHICH DRUGS ARE NEEDED

Viral infection, particularly herpes simplex
Bacterial and fungous infection
Cataracts (prophylaxis and therapy)
Glaucoma (prophylaxis and therapy)
Ocular malignancy
Ocular circulatory disorders (restoration of arterial and venous circulation)
Hemorrhage (to facilitate absorption of blood from ocular chambers)
Retinopathies of vascular and metabolic origin (prevention and reversal of ocular changes in atherosclerosis, hypertension, diabetes mellitus)

ly reverse constriction of the pupil produced by eserine, DFP or Phospholine iodide but has little effect on miosis induced by demecarium bromide (BC 48).

Anticholinesterases are important in the control of ocular signs of myasthenia gravis. 2-Pyridine aldoxime methiodide is helpful in overcoming overdosage with some of the anticholinesterases in therapy of myasthenia gravis. Often, patients with ocular myasthenia do not respond completely to the systemic administration of these drugs. Sometimes the ocular manifestations, such as ptosis, may respond to local administration of Prostigmine (figure 2). The Prostigmine may be placed in the eye as drops of a 5 per cent solution, or a pledget of cotton soaked in Prostigmine may be put into the cul-de-sac or applied as a wet pack over the lid for about 15 minutes. This is an uncomplicated way of testing for the presence of myasthenia and reduces the need for systemic injection of Prostigmine, with all its adverse effects, particularly if the patient does not have myasthenia. One can also use demecarium bromide (BC 48) (0.25 per cent) as drops in the cul-de-sac for this test. If the patient responds, you have achieved a positive therapeutic test for myasthenia gravis. If the patient does not respond, you may not conclude that the patient does not have myasthenia but should then test with systemically administered Prostigmine.

Ocular Conditions for Which Drugs Are Needed

I have mentioned a number of conditions which may be affected by some of the newer drugs used in ophthalmology. There are still a number of conditions for which therapeutic agents are needed (table 4).

At present there is no specific therapy for ocular viral infections. Vision is lost today because of such diseases as dendritic (herpetic) keratitis, for which therapy is largely nonspecific and includes approaches such as cauterization with iodine or silver nitrate. While we do have specific therapy for some bacterial and fungous infections, vision still is lost because of postoperative infections with resistant and virulent bacteria—and certainly some vision is lost to fungous infections in spite of amphotericin B.

There is no way to correct cataract except by operation. Glaucoma may respond to medical and surgical therapy, but preventive therapy for persons who seem to be predisposed to the disease is unavailable. Glaucoma tends to have a higher incidence among persons who have a family history of the disease, and it would be exciting to have some way of stopping the disease before it becomes established, with evidence of definite visual loss.

The chief treatment for ocular malignancy such as retinoblastoma and intraocular melanoma is enucleation. Chemotherapy, photocoagulation and diathermy have not been established as superior to radical surgery, although they offer some hope.

Inadequacy of ocular circulation, as seen in vascular occlusions, and macular degeneration do not seem to respond convincingly to anticoagulants or fibrinolysin. In traumatic intraocular hemorrhage and secondary hemorrhage, in addition to the problems of management, there appears to be no favorable method of producing rapid absorption of blood from the eye. We have to wait for nature to absorb the blood, and this predisposes to glaucoma, staining of the cornea, and loss of visual acuity.

There is general awareness of the major problem of diabetic retinopathy. Much has been written about it but little has been done actually to reverse the changes in the eye or even to prevent this serious complication in patients whose diabetes is well controlled.

There is no doubt that ophthalmology has shared and is sharing in the advances in therapy. Opportunities for future advances in this field are myriad.

The Accident Repeater

PSYCHIATRIC AND STATISTICAL CONSIDERATIONS

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Introductory Comment

Advances in the guarding of physical and mental health, together with the increasing speed and complexity of modern machines, have brought the problems of accident frequency and repetition into sharp focus in recent years. Controversial evidence, oversimplification and "fad thinking" about accidents too often confuse our efforts at understanding and treatment, as Dr. McLean and Mr. De Reamer point out.

In this brief article, the authors have ably reviewed major research in the field, interpreting their findings with a mature scientific perspective. Primarily, however, theirs is a clinical approach; they see the problems of diagnosis and treatment in accidents as no different from those of any other ill which befalls mankind. The individual as well as the entire situation, personal and environmental, emotional and physical, transient and prevailing, must be analyzed to determine the cause of an accident and prevent its recurrence. We know a little about what to look for, but we cannot here or elsewhere predict the diversities of individuals from the statistics of the group. Within this same flexible framework, the authors also effectively discuss problems of psychologic injury associated with accidents and ways of averting psychoneurotic complications in cases of simple stress reaction.—Franklin G. Ebaugh, M.D.‡

MAN drives as he lives," concludes McFarland.[1] This dramatic statement suggests that it is the driver's personality rather than his age, skill or physical fitness which plays the main role in accident causation on the highways. Since personality characteristics are relatively stable, one might then expect a relatively constant pattern of accident involvement in each individual. Tillmann and Hobbs[2] tended to support this idea in a provocative study of groups of drivers with either high or low accident rates. In their study, drivers with low accident records were serious, stable, well-adjusted individuals with well-integrated home backgrounds, while those with high accident rates were found to be aggressive and unable to tolerate authority at either a parental or a community level.

Relating accident propensity to personality

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appears to be a recurring theme of studies in this field. As early as 1919, Greenwood and Woods[3] demonstrated that the more accidents a man had had in the past, the more likely he was to have an accident in the future. It was, however, with Dunbar and associates' paper in 1936[4] that there began to develop some unanimity of opinion regarding the personality characteristics of the injury-prone personality. Since then, several hundred studies have explored further the relation between personality characteristics and proneness to self-injury. One of the most interesting concepts has come from LeShan,[5] who developed the concept of the "safety-prone" individual who never has an accident. He refreshingly and constructively explored the personality characteristics of the accident-free individual.

Purely statistical studies have demonstrated relations between seasons of the year and the incidence of accidental injuries. Length of experience in a dangerous job relates to the probability of a person's being injured while working on the job. Age and sex are also related to the probability of injury. Such research also notes that accidents tend to occur in clusters, not singly, for any given individual or group.

This paper will focus on observations stemming from research which relates psychologic and environmental factors to accidents and on studies of statistical factors in the accident syndrome. It is hoped that by combining these two sets of observations conclusions may be drawn which may be usefully applied in considering the apparently accident-prone patient. No effort has been made to present a comprehensive review of the literature or to report new research findings. Finally, we should like to examine the related problem of the meaning of the accident to the patient himself, with a view to earlier response to treatment of the injury.

Psychologic Studies

The physician may recognize that some of his patients appear more inclined to self-injury than others, but does he note this to be a lifelong pattern? Might not the more observant practitioner say, "Yes, I recall Sam Jones, who was involved in a whole series of accidents a few years ago. It was in 1956, I believe, just after he got married and while he was settling into a new job. I wonder what became of Sam's accident proneness? He hasn't had an accident in the past four years"? This physician, too, would find considerable support in the literature for the point of view that susceptibility to accidents may be episodic and related to the individual's total reaction to a life situation. Schulzinger[6] clearly pointed out that some individuals under particular patterns of stress appear to be more susceptible to accidents than are others. McLean[7] concludes that there are as many accident-proneness patterns as there are individual accident repeaters.

Most studies of accident repeaters are studies of young adults. What happens to these supposedly accident-prone people as they age? Certainly, they are not all killed in accidents. We can only presume that as they age chronologically they mature. This conclusion is in accord with Schulzinger's study, which called attention to the frequency of seemingly fixed patterns of accident repetition occurring only at certain emotionally stressful phases of a person's life.

In reviewing the literature, students of the psychology of accident repetition seem primarily concerned about the contradictory knowledge we have at hand on this subject. Unfortunately, the practical clinician must utilize what we do know in working with his patients who have accidents. From our own studies of injuries in the industrial populations, we have concluded that *the majority of accidents encountered are indeed the result of*

an individual personality interacting with the total life situation.[7-10] We have not found examples of the consistent, lifelong pattern of injury repetition. We have seen accidents as the result of reaction to stressful life situations. We have noted the contribution of environmental hazards to accidents.

Related Factors

Since there is a relation between types of personality and reactions to current stress, what are some of the factors which involve less stable individuals in patterns of accidents? If we presume this instability in some individuals and think about the situations which seem to cause accidents, we may better see the problem. There is accident potential in every situation. Resting in bed, for example, is loaded with hazards, such as the hazard of falling out and the hazard of falling asleep with a lighted cigarette. Any individual's ability to cope with these daily threats to his existence also varies from time to time, although the less stable personality may be more susceptible to injury. These two sets of factors —those in the environment and those in the individual—must be brought together for any accident to happen. It could be said that anyone who had an accident must have been, at the time, in a situation of accident potential. Yet, a person can be excessively liable to accidents for a long period without having a high record of injury. Between the accident's actually happening and the possibility of its happening is an interplay of a great number of factors which are difficult to detect.

In a mechanic with a lengthy record of freedom from accident, there developed unexpectedly what appeared to be an accident habit, with four major and six minor injuries. It took little investigation to discover an individual situation involving feelings of guilt because of a continuing extramarital affair which had its onset just before his first injury. The close relation between a major conflict and a resulting pattern of self-injury is not always as clear as it was here.

On the other hand, the environment may play the cardinal role. Consider the case of a young factory worker who was assumed to be accident-prone. We will call him Jim Brown. He had nine injuries in four months. One day, he had two accidents within an hour. He fell over a skid and bruised his leg. Returning to work from the clinic, he fell over the same skid. Was he injury-liable? Let us look at the causes of Jim's accidents. He fell over a skid that had been left in a poorly illuminated aisle at a blind corner. After the first accident, no one moved the skid. Jim's attention was diverted while he was explaining his injury to an associate, and he fell over the skid again.

Now, what about the other seven injuries? Two of them were eye injuries. Jim got sand in his eyes because his safety glasses had been improperly fitted. One injury was a small laceration of his little finger. Since he did not recall how it happened, perhaps a psychologic factor may have been involved. The four remaining injuries were burns on his right forearm. Investigation revealed that a protective flap had been removed from Jim's automatic welder. When asked why he had not reported the condition at least after the first burn, Jim said, "Oh, I don't like to bother my boss with such little things. The burns didn't amount to very much."

Whether or not Jim was accident-prone, certainly no one will deny that eight of his accidents could have been prevented by safe working conditions—keeping skids out of aisles, keeping flaps of the welder in place, and properly fitted safety glasses.

Personality, emotional stress, the feeling of guilt, and other similar factors can and do incubate accidents. Extramarital affairs will continue, employees will resent their bosses, and the entire population will represent various degrees of maturity. Likewise, stress will occur and recur, and people will continue to react to it. Merely trying to identify the accident-prone individual would be a small part of the total accident problem. Environmental factors, psychologic characteristics, and individual emotional reactions in intricate combination must be considered. The important point is that no one of these factors should be identified as being the principal cause of an accident. Obviously, those factors which can be controlled most easily deserve primary

attention. In other words, for an adequate understanding of the accident patient, one must consider not only the presenting injury but also the environment in which the patient was injured and the personality factors which were involved.

Statistical Studies

As indicated, most people move in and out of the accident-prone group according to age, emotional status, physical reactions, environmental factors and other conditions that vary with the passage of time. Several studies pinpoint factors which might statistically increase the likelihood of an accident. They deserve our attention. Some of the factors which were listed by De Reamer[8] include the following:

1. Young men have almost twice as many injuries as do young women.

2. More injuries are sustained in summer than in winter. The highest number occur in June, July and August, the least in February.

3. Accidents often occur in chain fashion, as if one injury acted as a trigger mechanism of another injury or series of injuries to an individual or to a certain group.

4. Less-experienced people seem to have more accidents than do more-experienced people.

These purely statistical studies provide significant guides to a positive approach to accident prevention. These key points emerge:

1. Attempts to control accidents by identifying and eliminating so-called accident-prone people are of little value. Only a very small percentage, if any, of the population can be identified as accident-prone all the time.

2. Awareness of accident potentials should be intensified during the summer months.

3. Both industry and the physician must give more attention to the development of safety-conscious living habits and attitudes during the preschool and school period. Emphasis must be placed on the development of safety principles that can be applied to any situation. For example, it would seem appropriate to encourage people to pause in a potentially hazardous situation before they act; to assume a situation might change; always to have a second line of defense; not to go beyond the point of no return; and to consider their physical, mental and emotional state in terms of accident potential.

4. To prevent the same type of injury from recurring, each injury should be analyzed at work and in the physician's office, and suggestions should be made to correct the immediate environmental and psychologic causes of the injury if possible.

5. Another major conclusion to be obtained from both the psychologic and the statistical studies may seem at first obvious. Accidents are *caused*. The physician's sensitivity to the wide variety of possible causes becomes important to him in the treatment of the injury and the prevention of future injury to his patient.

On the preventive side, one can work with a patient, urging greater awareness of his own individual accident potential during times when he is disturbed. The postaccident situation is useful with many patients as a time for counseling toward the prevention of future accidents. The avoidance of potentially hazardous situations when one is emotionally disturbed rings with even greater meaning following an injury. For instance, it is not always necessary for a man to drive an automobile immediately after a heated argument with his wife, nor is it wise for him to operate power tools in the home workshop when he is tired and irritable.

Meaning of an Accident to the Patient

A highly related clinical problem is the temporary personality disorders that often accompany or result from accidents and near accidents or "close shaves." The points we want to make will mean more if we can weave them into an example.

An electric equipment repairman had been employed by the same company for 32 years. In all those years, he had never missed a day of work because of illness. Then one day, through no fault of his, he happened to be at the scene of an explosion in the plant. His injury was a slight burn on the right forearm. One might expect that the man would normally have reported to work again within a day

or two. But this person was unable to use his arm for weeks, even though his injury was slight. He felt that he would not be able to resume his duties, and he blamed the company for his predicament. About four weeks after the accident, psychiatric treatment was begun, and he was soon able to return to work.

Drawing on this case, we want to make four points.

1. Although we describe these disorders as temporary or transient, such reactions can lead to more serious complications, even to prolonged emotional disability, unless properly treated.

2. Without some understanding of what the accident means to the injured person, simple mechanical treatment of the injury itself does little to treat the stress reaction.

3. If we are really going to help such a person, we must know more about what happened to him; we must know something of what is presently going on in his life, as well as something about his personality.

4. The longer we wait before treating this type of disorder, the more difficult it is to treat; in the meantime, if we allow the injured person to return to work in this condition, we run the risk of exposing him to another accident.

We all recognize that any serious injury or near injury may injure a person emotionally as well as physically, even the healthiest of us. A wide variety of symptoms may develop as stress reactions, but the following are the most frequent characteristics. Whether or not the patient sustains a physical injury, characteristic symptoms of anxiety quite generally develop. These may include increasing irritability, sensitivity to noise and sudden change, repetitive dreams of a dangerous situation, and marked fears of returning to the situation in which he was overwhelmed.[11]

These symptoms are, in reality, defenses which automatically develop in the individual in his struggle to adjust to an overwhelming situation, to assimilate a frightful experience into his experience. Some of us can adjust to these experiences quickly; others cannot. We should not confuse these reactions with the neuroses and the psychoses. When promptly and adequately treated, these conditions clear rapidly. Even without treatment, such reactions are relatively transient. However, this kind of condition can develop into a psychoneurotic reaction.

As we have said, reactions to any stressful event are determined not only by the event but also by the personality of the individual involved. The total life situation in which he finds himself also gives particular meaning to the events which trigger his symptoms. For an injury or a "near miss" to trigger such a reaction, it must have great personal meaning. Therefore, if we are to be of help to such a person, we must know something of what is presently going on in his life, as well as something of his personality.

Most of us realize, for instance, that we are safer drivers when we are cool, calm, sober and untroubled. When we are angry at the world, upset, or otherwise less controlled in our feelings, we become a danger to ourselves and to others on the road.

Looking into the life situation of the repairman, we find that he was a dependent person, passive and quiet, who worked ably for one foreman during the 10 years before the time his case came to light. His relation with his foreman would best be described as close. The repairman leaned heavily on an authoritative, strong "boss."

Three months prior to the accident, the repairman's wife died. He managed to recover from this severe personal stress and adjusted to his new life in part by clinging to his relation at work and to the steadying influence of the job itself. The explosion in which he was burned slightly seriously injured his foreman, who was unable to resume his duties. The major support of the repairman's life was withdrawn. He had become completely dependent, was angry at the world, and blamed his company for his predicament. Psychiatric referral was necessary to effect fairly rapid improvement and to assist in returning him to work.

Summary

Research into concepts of accident proneness has been fruitful. However, in reviewing

the literature, students of the psychology of accident repetition seem primarily concerned about the contradictory nature of the knowledge we have on this subject. Such studies have pinpointed many personality characteristics which often lead to an accident.

We must also think about situations which seem responsible for accidents to see the problem in a clearer light. There is indeed accident potential in almost every situation. However, two sets of factors—those in the environment and those in the individual—must be brought together for any accident to happen. Between the accident's actually happening and the possibility of its happening is an interplay of a great number of factors which in their total are often subtle indeed. The effort to understand all factors responsible for an accident becomes of paramount importance in treating injuries and preventing future accidents.

It is our observation that past efforts to associate a large number of accidents wholly with personality characteristics and conscious and unconscious thought processes may have been misleading. This does not mean that these factors may be ignored; they are important. But, we must give more attention to the total accident picture. In some cases psychologic investigation is indicated, but often the simple matter of moving a skid may be the more practical solution to accident prevention.

Finally, a highly related clinical problem is the temporary personality disorders that often result from accidents or near accidents. A major section of this paper brings this problem into sharper focus.

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Practical Dietary Control of Serum Cholesterol in Free-Living American Men Aged 50 to 59

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IN 1957, the death rate from atherosclerotic heart disease per hundred thousand men aged 50 to 59 years in New York was 616. A public health problem may be said to exist when this rate exceeds 350 per hundred thousand men.[1] Keys[2] has indicated that in all countries and communities in which serum cholesterol determinations in middle-aged men showed an average level over 220 mg. per cent, a problem of coronary heart disease existed. In communities in which the average serum cholesterol in this age group was below 200 mg. per cent, there was no major problem of coronary heart disease.

The rise in serum cholesterol with age, noted in adults in the more affluent Western cultures, is not inevitable, for it is not found in the lean and hungry populations of the nonaffluent cultures. It also might be observed that in this latter group there is no corresponding increase in body weight with age, as is found in Western cultures.[3]

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A study by the Public Health Service[4,5] of the population aged 45 to 62 residing in Framingham, Massachusetts, revealed that men with serum cholesterol levels below 225 mg. per cent proceeded from normal hearts (with relation to coronary heart disease) to clinical coronary heart disease at the rate of 13 per thousand after four years of observation at biannual intervals. This is to be compared with an incidence of 80 per thousand per four years in men entering the study with

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cholesterol levels over 260 mg. per cent. Nonobese men revealed an incidence of new attacks of coronary heart disease amounting to 28 per thousand per four years; the incidence was 57 per thousand per four years in obese persons. Hypertensive subjects had an incidence of 100 new attacks per thousand persons per four years, compared with 17 in normotensive persons. Expressed more concisely, clinical coronary heart disease developed in the over-all Framingham population studied at a rate of 43 per thousand per four years; it developed in subjects with normal cholesterol, normal blood pressure and normal weight at a rate of 10 per thousand per four years, and in those with two or more abnormalities in the aforementioned parameters at a rate of 143 per thousand per four years.

If the risk of the development of coronary heart disease in obese hypercholesteremic men aged 45 to 62 years is 14 times greater than in men of normal weight with normal cholesterol levels, and if diet can alter both of these abnormalities, it would follow that a study of the attack rate following dietary therapy would be of clinical interest.

In February 1957, the Diet and Coronary Heart Disease Study Project of the Bureau of Nutrition, Department of Health, City of New York, usually known as the Anti-Coronary Club,[6-8] was originated by an executive order of the Commissioner of Health of the City of New York. Our over-all objective was to investigate a dietary approach to the prevention of coronary heart disease. This was to be done by developing practical diets for use by the general public which would be nutritionally adequate and palatable, would be composed of American foods available in every community, and which would lower the serum cholesterol level in those free-living, ambulatory subjects who modified their diets. The main objective would be accomplished when we could determine that a favorable change in the serum cholesterol level produced and maintained by diet was associated with a favorable change in morbidity and mortality from coronary heart disease, particularly in men less than 65 years of age.

The work of Kinsell and associates[9] provided an aid to a practical dietary approach which was later confirmed by others;[10-12] namely, that in persons trained in a metabolism study ward or taught to follow formula diets, the substitution of oils high in polyunsaturated fatty acids (corn, cottonseed, marine, safflower, soybean, sunflower) for the dietary saturated fats would lower the blood cholesterol. This permitted us to construct a diet in which foods with predominantly saturated fatty acids (butter, whole-milk cheeses, ordinary margarines and hydrogenated shortenings) and foods containing them in significant amounts (beef, pork, lamb and eggs) are eliminated or reduced in quantity. These foods are replaced by those with predominantly unsaturated types of fatty acids (vegetable oils, fish, most nuts and grains) and with leaner meats such as poultry and veal. Such a diet, which we term "prudent," contains about 30 to 33 per cent of the total calories as fat and has a ratio of polyunsaturated fatty acids to saturated fatty acids (P/S ratio) of 1.25 to 1.50 (table 1).

The overweight subject is placed on a diet averaging 1600 calories and containing 19 per cent of calories as fat. When weight reduction is completed, this diet is transformed into the prudent diet by the addition of 45 gm. of a vegetable oil high in linoleic acid, such as corn oil, plus additional calories when needed from bread, fruit and vegetables.

The Prudent Diet

Instructions for the prudent diet pattern are as follows. Consume adequate amounts of high-grade protein foods at each meal. The sources for these include cottage cheese (preferably skim-milk cottage cheese), fat-free milk, chicken, turkey, veal, leaner cuts of beef, mutton, lamb, pork, fish, sea food, and egg whites. All visible fat should be removed from the meats and poultry.

Remember, there are 21 meals each week. Therefore, from this list, include fresh or canned fish or sea food in at least five meals each week. Lunch is a good meal for this. Do not be limited to the leaner fish; include fat fish as well, as they are good sources of polyunsaturated fatty acids. Bake, roast, broil or

TABLE 1

APPROXIMATE COMPOSITION OF THE PRUDENT AND THE REDUCING DIETS

NUTRIENT	PRUDENT DIET* (GRAMS)	REDUCING DIET† (GRAMS)
Protein	130-150	140
Carbohydrate	225-280	180
Fat	66-97 (30-33%)	33.5 (19%)
Saturated fatty acids	19-21 (7-8%)	13.8 (7.8%)
Monounsaturated fatty acids	25-26 (8-9%)	11.4 (6.5%)
Polyunsaturated fatty acids	20-23 (9-11%)	8.3 (4.7%)
P/S ratio	1.25-1.50	0.6

*2000 to 2700 calories.

†1600 calories.

boil meats and poultry. Fish may be fried in a high-P/S ratio vegetable oil (corn, cottonseed, safflower, soybean, sunflower). Use veal or poultry in four meals each week or oftener. Use four 3 to 4 oz. servings of beef, lamb, mutton or pork, not exceeding a total of 16 oz. each week. For the other eight meals each week use cottage cheese or egg whites, an occasional serving of liver, or additional servings of fish, sea food or poultry. Unless instructed otherwise, you may use up to four whole eggs each week.

You may use whole milk for coffee, but otherwise restrict the use of milk to nonfat varieties, such as fresh or reconstituted skim milk, fat-free buttermilk, or evaporated skim milk. When instructed, you may emulsify a high-P/S ratio oil with your skim milk with a high-speed electric mixer. Five and one-half cups of cold water, 2 cups of powdered skim milk, 2⅓ oz. of vegetable oil (corn, cottonseed or peanut), and between 4 and 13 drops of butter flavor, depending on individual preference, will make 1½ qt. of "milk." Directions for mixing are as follows: Place the cold water in a 2 qt. narrow-mouthed fruit jar. Stir in the powdered skim milk. Add the oil and butter flavor. Attach the beater head of a high-speed electric blender to the 2 qt. jar. Blend at high speed for seven minutes.

The mixture should be stored in the refrigerator. After several hours most of the foam will have settled. In pouring the milk, the remaining foam may be held back with a tablespoon. Sometimes, a little creamlike material will rise to the top of the jar, but this can be readily dispersed by shaking.

When varying the total quantity of the recipe, the blending time as well as the individual ingredients must be varied in direct proportion to the total quantity. Individual ingredients may be varied slightly to suit the taste. The preparation contains about 23 calories per ounce.

A palatable 20 per cent creamlike material which can be used in coffee can be made by mixing 1 cup of cold water, ⅓ cup of skim-milk powder, 2 oz. of vegetable oil, and 4 to 12 drops of butter flavor for two minutes in a pint jar.[13]

In addition to the ½ oz. of high-P/S ratio vegetable oil used in food preparation, consume a minimum of 1 oz. of oil at the table each day. This may be used in salad dressings and on vegetables, emulsified in milk, or added to cereals or desserts. All commercially available mayonnaise and salad dressings may also be used, since they are made with liquid salad oils that are high in linoleic acid and low in saturated fatty acid content. In addition, you may use a 10 gm. pat of a high-P/S ratio margarine daily as a table spread. When a solid fat is preferred in cooking or baking, use a high-P/S ratio margarine or cooking fat, preferably one with a P/S ratio of about 1.5. Never use the conventional, partially hydrogenated types of margarines, cooking fats or butter.

Do not eat butter; conventional, partially hydrogenated margarine and shortening; lard or cream or foods containing them in large amounts, such as most cakes and pastries. In place of butter or ordinary or partially hydrogenated margarine, use a high-P/S ratio margarine; in place of shortening, use a high-P/S ratio vegetable oil or a high-P/S ratio margarine, and, in place of cream, use an emulsion of a high-P/S ratio oil.

In over three years' experience, we have found that the more than 600 men partici-

pating in this experiment have encountered the following difficulties in adhering to the prudent diet.

1. The giving up of pastries made with highly saturated fat, such as Danish pastry, coffeecake, poundcake, "plain" cake, cookies and pies, seems to be a real deprivation for many people and causes the most frequent difficulty. These products need not be prohibited for the person whose wife is willing to make them with vegetable oil or a linolate-rich (high-P/S ratio) margarine. However, since most modern housewives do not or will not bake their own pastry, the subjects are limited to angel cake, spongecake, Holland honey cake, almond macaroons and a few other low-fat, locally available baked goods.

2. Limiting the size of portion and frequency of serving of meats containing high proportions of saturated types of fats, such as beef, mutton and pork, also is difficult. It seems that many men in our affluent society have become accustomed to consuming 8, 10 or 12 oz. portions of these products. In a balanced diet containing adequate calories, no normal subject needs more than 3 or 4 oz. of animal flesh daily. This amount twice daily is more than adequate, especially when skim milk and cottage cheese are included.

3. Prohibition of ice cream is deprivation for many persons, although this ranks well below the first two complaints listed. Here, water ices, with a very occasional sherbet, are the best substitutes.

4. Restaurant meals present difficulty for some people, but this difficulty is more apparent than real. If a person can afford to eat at restaurants where the food is prepared to order, no problem exists. In restaurants and cafeterias where the food is prepared on a large scale, the problem is much greater. In the latter case, the entree should be fish, sea food or poultry, which should be boiled, broiled or baked. The dessert should be limited to fruit.

5. Hard cheeses of all varieties present a minor difficulty for a few people. For those who must have hard cheese, 1 oz. may be substituted occasionally for half of the beef, mutton or pork allowance, or this entire allowance may be replaced by 2 oz. of cheese.

Prohibition of butter and whole milk has presented no difficulties. Butter is one of the easiest foods to replace in the diet, since so many substitutes are available, e.g., proper margarine, mayonnaise, cottage cheese spreads moistened with skim milk, or skim milk mixed with vegetable oil.

Procedures of the Study

The subjects in this study are male volunteers less than 60 years of age from all segments of the New York population who are willing to follow our dietary recommendations over a long period. They are physically capable of participating in the study and have sufficient time available during working hours to do so. Our workup consists of a thorough medical history and physical examination; an electrocardiogram; roentgenograms of the heart, abdominal aorta and iliac and tibial arteries; glucose tolerance tests; and determination of control blood cholesterol levels. Cholesterol levels are taken at biweekly intervals during a control period of one to three months while the patient follows his usual diet. We have called the average of these cholesterol determinations the bench-mark level. In our present study, the control level of serum cholesterol for the first 400 men, 50 to 59 years old, averaged 259.9 mg. per cent, with 19.5 per cent under 220 mg. per cent and 7.7 per cent under 200 mg. per cent.

The laboratory determinations of the blood cholesterol require a meticulousness that is not always found in many hospitals and commercial laboratories. A technical error of more than 5 per cent should not be accepted, and exceptional laboratories with high standards can have a technical error as low as 3 per cent. On this basis, deviation in blood cholesterol of 10 per cent or more probably represents a significant difference.

During the control period, a dietary evaluation is made. At an orientation lecture which precedes the subject's entrance into the study, a nutritionist explains in detail the method of recording the amount and kind of food and beverage consumed for a week.

There are two parts to our dietary evalua-

tion. First, a written seven day diet record is obtained from each patient for the week preceding a diet conference with the nutritionist. Secondly, a recall diet, which represents an average week as far back as the patient's memory serves him, is elicited from the patient in the presence of and with the assistance of his wife. At the diet conference, the written record is reviewed with the patient and his wife, and food models of known quantities are used to help gauge amounts. Recipes are reconstructed with the wife, since necessary details are often omitted, e.g., the sugar and milk in coffee and fats used in food preparation. Both recall and record diets are calculated in terms of calories and approximate composition of protein, carbohydrate, fat and various essential minerals and vitamins.

After the diet record is completed, each subject is then classified according to whether he is underweight, of normal weight, or overweight. Tables of average weight at age 25 to 29 years, skin caliper measurements, the ruler test and the general appearance[14] are used as criteria for determining the weight status. In general, subjects 15 per cent or more above their desirable weight are placed on a reducing regimen.

Results

The prudent diet is effective in lowering the blood cholesterol in about 80 per cent of subjects with bench-mark (control) levels in the upper third (270 mg. per cent and over), in 60 per cent of those in the middle third (230 to 269 mg. per cent) and in 30 per cent of those in the lower third (under 230 mg. per cent). It is thus effective in lowering the blood cholesterol in about 70 per cent of "high-risk" subjects. The course of serum cholesterol of 97 men of normal weight aged 50 to 59 years during the bench-mark period and at the end of six months on the diet is marked by a fall in cholesterol from the bench-mark level of 253 mg. per cent to 224 mg. per cent after six months ($t = 5.16$, significant beyond the 1 per cent level).

The fall in cholesterol has been evaluated by dividing the group into thirds. In the highest third, 34 men show a drop from 298 mg. per cent to 253 mg. per cent; in the middle third, 32 men show a fall from 249 mg. per cent to 224 mg. per cent, while, in the lowest third, 31 men show a drop from 207 mg. per cent to 191 mg. per cent after six months on the prudent diet. The fall in each third is significant beyond the 1 per cent level. Those patients with a diagnosis of coronary artery disease in this group responded the same as those with no clinical evidence of coronary artery disease but with similar bench-mark levels. It is to be noted that whereas 25 per cent of the group had a serum cholesterol under 220 mg. per cent during the control period, this figure rose to 50 per cent after six months on the diet.

Fifty-four men in our 50 to 59 year age group have completed one year of adherence to the diet. The two highest groups show a maintenance of the cholesterol level attained at the end of six months, while the lowest group shows a small rise in cholesterol level, which is not statistically significant at the present time.

Our overweight subjects in the 50 to 59 year old group comprised a starting group of 211 men. Of these, 111 (52.6 per cent) adhered so rigidly to the prescribed reducing diet as to achieve a performance index of 85 or better during the first 10 weeks of observation. (The performance index is the ratio of the actual to the predicted weight loss.) Their average serum cholesterol dropped from 261 to 225 mg. per cent by the end of six weeks and remained level thereafter ($t = 6.78$, highly significant). Of the 111 men, 97 reduced to desirable levels; 75 have been maintained on the prudent diet for at least six months, and 56 have been maintained for at least one year, with the average serum cholesterol remaining level.[15]

Therefore, with respect to effect on serum cholesterol, strict adherence to the prescribed reducing diet yielded results in overweight men similar to those obtained by the use of the prudent diet in men of normal weight. Further, maintenance of weight after successful weight reduction by use of the prudent diet serves to maintain the lowered serum cholesterol level and prevents the rebound experi-

enced in the more usual types of reducing and maintenance diets.[16,17]

By thirds also, the results in the overweight men are similar to those obtained by use of the prudent diet among men of normal weight. In the upper third, the average serum cholesterol level of 307 mg. per cent fell to 260 mg. per cent; in the middle third, a level of 257 mg. per cent fell to 220 mg. per cent, and the level of 207 mg. per cent in the lower third fell to 189 mg. per cent. The lower limit reached by each third corresponds very closely to its counterpart in the men of normal weight. The major point of difference lies in the time necessary to achieve the low value. Six weeks were required on the reducing diet, compared with five to six months on the prudent diet. It is to be noted that only 21 per cent of the overweight group had serum cholesterols below 220 mg. per cent during the control period; after 10 weeks on the prescribed reducing diet, this figure had doubled to 42 per cent.

Summary

These results indicate to us that the first two objectives of our study have been met; namely, that a diet, acceptable and palatable to motivated subjects, has been constructed to which a majority will adhere and which will lower the blood cholesterol significantly, if not optimally. The success of this type of diet has been confirmed by Stamler.[18]

We now have to consider the effects of these results on the attack rate from coronary heart disease. Toward this end, we are collecting man-years of experience in our study group and in a contemporary control group gathered from our city cancer detection clinics. These control subjects have been chosen because they are also health-motivated, albeit toward another disease. At our present rate of collection of data, we hope to be able to make a first examination of our records in approximately two years.

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Pitfalls in Anesthesia for Emergency Pediatric Surgery

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RECENT studies[1,2] have pointed to an inordinately high mortality rate associated with pediatric anesthesia. The reason for this high mortality rate was not always clear. In most instances the children were not poor operative risks. The real tragedy of the matter is that most of the deaths occurred in children who were *good* risks and in whom the surgical procedures were relatively minor and of short duration. Most of the deaths were preventable. Many occurred during so-called emergency surgery.

Provision of safe anesthesia in emergency situations is always difficult. The problems are multiple. The patient frequently is terrified, uncommunicative and resistive. The seriousness and extent of the illness or injury are difficult to assess in the face of this lack of cooperation, and the history of events preceding the emergency, such as ingestion of food, is at best usually sketchy. These and other considerations help explain the relatively high incidence of complications encountered when anesthesia is administered under emergency conditions.

This paper will review the basic principles of management of pediatric anesthesia in emergency situations, with specific attention to the most common pitfalls. It is my hope that it will stimulate the physician to conduct a critical analysis of local practices and will serve as a guide in establishing safe anesthetic practices in a field which obviously requires considerable attention if the mortality figures are to be improved.

The pitfalls can be classified under two main headings: errors in judgment and errors in management.

Errors in Judgment

1. Assessment of the urgency of the surgical procedure—Actually there are only three truly urgent emergencies in pediatric surgery.

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They are respiratory obstruction, uncontrolled hemorrhage and severe head injury. Obviously these situations must be managed swiftly. Most others, however, allow at least some time for evaluation of the patient and application of whatever preparative treatment seems indicated. The child should *not* be rushed to the operating room from the physician's office or from the emergency room. Too often the misguided belief that immediate surgical treatment is all-important plunges us into situations that are unwarranted and dangerous. It is well known that anesthetic complications occur with much greater frequency in patients who are inadequately prepared for surgery.[3]

The evaluation need not be detailed but should include at least the basic requirements of a history and physical examination. The anesthetist should always have an opportunity to assess the patient. The family physician may know the patient well and may have cared for him since birth, but the person responsible for administering the anesthesia too often knows little about the patient. Failure to obtain an adequate anesthetic history frequently leads directly to anesthetic complications. For example, cyclopropane or curare unwittingly administered to an asthmatic child may result in an asthmatic attack which endangers the life of the child and seriously compromises the success of the surgery. Or barbiturates given for premedication or anesthetic management may precipitate a paralytic crisis in a patient with porphyria. Sufficient time should be allowed to plan the anesthetic procedure and to gather the equipment required to provide the safest anesthesia possible under the circumstances.

Several other benefits accrue from this calculated "delay." The child can become acclimated to the hospital surroundings; appropriate sedation can be administered and its adequacy judged.

2. Assessment of the degree of toxicity—The mortality statistics referred to earlier cite many cases of appendical perforation in children who were otherwise healthy. Severe anesthetic difficulties often arise in such cases and the death rate is surprisingly and alarmingly high. If the toxicity which so often accompanies appendical rupture is not recognized and treated prior to operation, the patient's ability to withstand the stress of anesthesia and surgery is diminished. There is no question that toxicity plus anesthesia is a lethal combination and should be avoided whenever possible; and if the anesthesia is not conducted properly the danger is even greater.

Three of the best guideposts to the presence of significant toxicity are hyperpyrexia (over 102° F.), dehydration, and tachycardia out of proportion to that normally expected in a child who is excited and has just been admitted to a hospital. These things can be assessed without intricate laboratory data. Unless the circumstances are desperate, the toxicity should be controlled before surgery is undertaken. The child should be cooled by some means such as ice bags or a cooling blanket until the temperature is less than 102° F. and until the tachycardia subsides. Some form of sedation is usually appropriate as a supplement to these steps.

When tachycardia and hyperpyrexia are present, it usually is best to omit the conventional administration of atropine an hour before surgery because this drug may exaggerate the tachycardia and the hyperpyrexia. Rather, a small intravenous dose should be given when the patient is brought to the operating room. This will provide the maximal drying effect without unnecessary elevation of pulse rate prior to the operation.

3. Assessment of the child's food intake—A third common error in judgment stems from difficulty in assessing the child's recent food intake. The mother's statement can be helpful in this regard but is often misleading. She can usually describe the child's menu for the last 12 hours and can tell when the child last ate a meal. But children are habitual "snackers," and the child's stomach frequently will contain other food (apples, popcorn, etc.) which the mother does not know about. Remember also that gastric motility ceases almost instantly with the onset of an acute illness or injury, so that, although three or four hours have passed since the insult, any food which was in the stomach at that time

will remain undigested and will not pass on into the small bowel for many hours. Thus, regurgitation of undigested food is a common reaction when an anesthetic is administered.

The methods usually recommended for evacuating the stomach are not very reliable. A nasogastric tube will drain off fluid but will not remove the heavy material, the unchewed large particles often present in the child's stomach. Emetic drugs such as apomorphine are superior since they produce a more profound and continuous evacuation of the stomach. However, the nature of the illness or injury may preclude the use of either of these methods because of the retching and struggling that they impose.

Errors in Management

1. Failure to prevent aspiration of stomach contents—Ignorance of the hazards associated with the full stomach is a common predisposing factor leading to aspiration, but frequently this complication is traceable to the improper choice of anesthetic agent or technic.

Local or regional anesthetic technics should be employed whenever feasible since these methods preserve the normal laryngeal reflex against foreign material. In infants especially, local anesthesia (employing dilute concentrations) combined with the use of mummying or the "gingerbread boy" provides adequate surgical conditions with complete safety. A very useful technic and one that is not difficult to apply in most children is the axillary nerve block which provides anesthesia of most of the branches of the brachial plexus; it is accomplished by injecting an anesthetic agent about the axillary artery, which can be palpated in the axilla close to the lower edge of the pectoralis major muscle. All the major nerves innervating the arm are clustered about the artery at this point and are easily anesthetized. A 25 gauge needle is used, and the only discomfort the child experiences is the initial pinprick. If the patient is lightly sedated he usually will accept this block without difficulty. Burnham[4] has described its use in children as young as two years. With this block it is possible to reduce fractures and repair lacerations of the hand and arm without endangering the child who has a full stomach.

When general anesthesia is mandatory, endotracheal intubation is advisable to circumvent the problem of aspiration during surgery. *Induction* of general anesthesia usually will not cause vomiting if it is carried out smoothly and without hypoxemia. The danger of vomiting and aspiration is very much greater *during emergence* from anesthesia, and in this fact lies the key to the proper use of the endotracheal tube in these cases. The tube should be left in place until the child has reacted fully from the anesthetic, is moving about, and is actually trying to remove the tube himself. If this is done, there need be no fear of vomiting during emergence since the presence of the tube in the trachea will preclude aspiration of gastric contents.

If the physician lacks experience with endotracheal technics, it is advisable *not* to attempt intubation in such cases. Rather, an anesthetic technic should be employed which will allow for retention of glottic reflex control. This requires maintenance of a *light* plane of anesthesia, usually with a gaseous or volatile agent (viz., cyclopropane or ether). In this manner, even if vomiting occurs, the laryngeal reflexes will be sufficiently active to prevent the aspiration of regurgitated material into the tracheobronchial tree. It should be emphasized that only *light* anesthesia will provide this protection. It has been suggested that the proper depth of anesthesia is present in these circumstances when moderate tone remains in the muscles of the arm and the child flexes his elbow and wrist joints in response to strong surgical stimulation.[5] The use of the new antiemetic drugs as adjuncts in forestalling vomiting under these circumstances may prove valuable but as yet no reliable data are available on this phase of their application.

"Crash" induction of anesthesia with intravenous barbiturates and relaxants is extremely hazardous except in the hands of an anesthetist with considerable experience in endotracheal intubation. It is not a suitable method for the tyro or "occasional" anesthetist, because sudden regurgitation may

flood the airway with vomitus, and unless a tube can be inserted into the trachea quickly the patient may not survive.

2. Inadequate observation of the patient—There is a dangerous tendency for anesthetists to become lulled into a false sense of security by the relatively wide margin for error that exists in the conduction of anesthesia in most healthy adults. Excessive anesthetic dosage, blood loss, or disturbances of respiration such as partial obstruction or depressed ventilation usually provoke satisfactory compensatory mechanisms in the adult which allow adequate time for even a belated correction on the part of the physician. In children this is not the case. The margin of safety is narrower; such diversions from the norm must be prevented or dealt with promptly. Therefore the anesthetist cannot afford to be complacent or lackadaisical in his observation of the pediatric patient under anesthesia.

The signs of anesthesia should be checked closely and the plane kept light, as mentioned previously. The eye signs, the respiratory rate and the muscular tone provide adequate guides in judging depth of anesthesia. When anesthetic depth must be increased, this should be done slowly, with close attention paid to the clinical changes which may accompany such an increase.

The patient's ventilation should be observed carefully. This means, of course, that a patent airway, which is all-important in maintenance of good ventilation, must be maintained at all times. An airway which is partially obstructed increases the work of breathing markedly and tends to aggravate the pre-existing toxicity. Hypercapnia and hypoxemia (the ultimate consequences of poor ventilation) are well-known predisposing etiologic factors in cardiac arrest. Ventilation usually is adequate if the anesthesia is light and the patient is receiving an anesthetic that does not depress respiration excessively. Light ether, nitrous oxide and fluether (azeotropic mixture of fluothane and ether) are the only agents which do not depress respiration.

The circulation must be watched just as closely. It is surprising how often infants are anesthetized without any attempt being made to measure the blood pressure. While blood pressure measurement in infants admittedly is difficult, anyone who administers anesthetics to infants should make such measurements repeatedly; relative changes in blood pressure are important in the assessment of the patient's condition during surgery. A small stethoscope diaphragm taped over the precordium allows the anesthetist to monitor the heart rate constantly. A somewhat more refined and more modern appliance for monitoring the pulse is the esophageal stethoscope, which is simply a catheter with a small rubber balloon glued over the ports; it can be inserted via the nose or mouth into the mid-esophagus so that it lies directly behind the heart. More complex electronic monitoring equipment is not necessary. The blood pressure cuff and stethoscope provide sufficient information concerning the child's circulation. If these functions are observed frequently (continuously, whenever possible) early changes will be appreciated and appropriate therapy can be applied before serious cardiovascular depression ensues.

3. Errors in fluid and blood replacement—A route for intravenous therapy should be established in every patient who is to receive a general anesthetic and who is to undergo any extensive surgical procedure. This assures a ready route of blood replacement and drug therapy. If percutaneous venipuncture is not possible, we perform a cutdown. The little additional time and expense involved is a small price to pay for the safety provided, and unless the procedure to be performed is extremely minor I think it is a good investment.

A graduated buret (figure 1) is useful in preventing overhydration of infants. Only a small predetermined amount need be placed in the buret at one time; this eliminates the hazard of inadvertently infusing a larger amount from the conventional fluid container. A careful appraisal should be made frequently of the blood lost during the procedure. The sponges used to collect the blood from the operative field should be weighed. This is a simple and inexpensive way to judge the blood loss.[6] By knowing the weight of the dry sponges and by weighing them after they are

wet, a simple subtraction yields a reasonable estimate of the amount of blood lost. The blood collected by the suction apparatus should also be measured if it is significant. The amount which is absorbed on the drapes and gowns must be estimated.

4. Miscellaneous problems—Finally, some of the miscellaneous problems that arise are hyperthermia, hypothermia and gastric distention. Hyperthermia occurs less frequently than it did formerly, since most operating rooms today are air-conditioned and the lighting appliances have better heat dispersion. When hyperthermia does occur, however, it is an insidious and dangerous complication. Increased body temperature in an anesthetized patient (especially when ether is employed) may produce generalized convulsions; this is especially likely if carbon dioxide accumulation has occurred due to hypoventilation. These convulsions are extremely lethal. It has been estimated that about 50 per cent of children who have severe convulsions under anesthesia do not survive. It is obvious that such a serious complication should be prevented whenever possible.

Accidental hypothermia during surgery is common nowadays,[7] especially when the chest or abdomen is opened widely in a cool operating room. The body temperature frequently will fall to 90 or 91° F. Such hypothermia introduces the hazards of low blood pressure and weak and inefficient heart action, and causes delayed return to normal feeding patterns in the postoperative period. Fortunately in the presence of such hypothermia the child can better tolerate reduced circulation or blood pressure, but such conditions are quite unphysiologic and should be avoided. The rectal temperature should be measured frequently or continuously during prolonged surgical procedures; preventive measures such as the application of hot water bottles or a mechanical heating-blanket device to maintain the child's temperature are recommended.

Gastric distention occurring during surgery is quite common and in general is poorly recognized. Air swallowing occurs in almost every child during the early phases of induction. The aerodilation usually is increased during maintenance of anesthesia if respirations are augmented by pressure on the breathing bag. This complication is significant, since the child cannot breathe well due to the compression that the gastric air places on the diaphragm; carbon dioxide accumulation and its sequelae are the obvious results. The treatment of this gastric distention is simple and effective. A small catheter should be passed into the stomach; gentle manual pressure on the epigastrium will expel the gastric air.

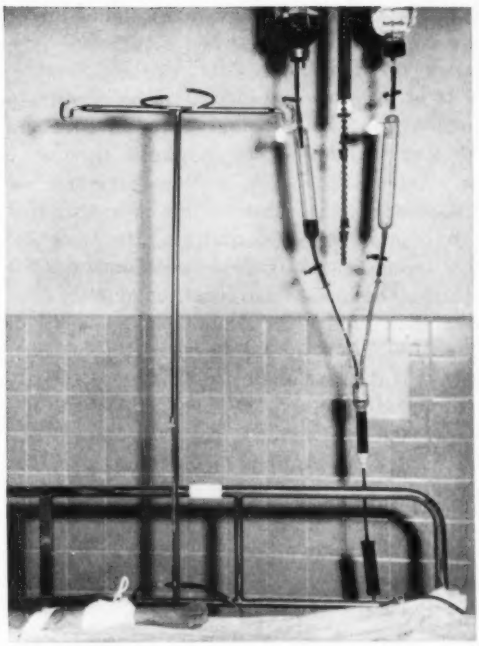

FIGURE 1. Burets for administration of blood and fluid to infants and small children.

Conclusion

Increased knowledge of fluid and electrolyte balance, improved surgical technics, and widespread availability of the antibiotics have improved the prognosis in the critically ill child immensely. But it is clear that real progress in reducing the appalling mortality rate that still exists in pediatric surgery hinges on improving anesthetic management.

The points discussed represent the major defects in anesthesia for emergency pediatric

surgery. Certainly, many more subtle errors are committed which, when summated, seriously compromise the safety of the patient.

It is the responsibility of every physician involved in the surgical care of children, whether he administers anesthesia personally or whether he simply is responsible for its administration, to observe the basic tenets of safe management and, above all, to recognize the limitations of available personnel and facilities. The cases which contributed to the high mortality cited were doubtlessly managed in good faith; but we are faced with the naked fact that the vast majority of these accidents and misadventures were preventable. It is obvious then that we must strive to augment our knowledge in this area so that these valuable lives may be spared.

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MEETINGS *and Postgraduate Courses*

American Cancer Society, Inc., New York: Scientific session on the physician and the total care of the cancer patient, to be held October 23-24 at the Biltmore Hotel. For further information, write to: Professional Education Section, American Cancer Society, Inc., 521 West 57th Street, New York 19.

American College of Chest Physicians: Postgraduate courses for 1961:

Cardiopulmonary problems in children, Brown Palace Hotel, Denver, July 24-28
Industrial chest diseases, Warwick Hotel, Philadelphia, September 25-29
Clinical cardiopulmonary physiology, Sheraton Hotel, Chicago, October 23-27
Recent advances in the diagnosis and treatment of heart and lung diseases, Park Sheraton Hotel, New York, November 13-17
Recent advances in diseases of the chest, Statler Hilton Hotel, Los Angeles, December 4-8

For further information, write to: Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11.

American College of Surgeons: Meetings in 1962:

Sectional meetings:
Surgeons and graduate nurses, Los Angeles, January 29-February 1
Detroit, March 5-7
Memphis, March 26-28
Washington, D. C., April 16-18
Annual clinical congress, Atlantic City, October 15-19

For further information, write to: Dr. William E. Adams, Secretary, American College of Surgeons, 40 East Erie Street, Chicago 11.

Canadian Association of Physical Medicine and Rehabilitation, Saskatoon, Saskatchewan: Ninth annual meeting to be held August 24-26, at the Bessborough Hotel. For further information, write to: Dr. Maurice Mongeau, Office of the Secretary, Canadian Association of Physical Medicine and Rehabilitation, 6265 Hudson Road, Montreal 26, Quebec.

Institute for Research in Hypnosis, Cleveland: Workshop on pain, pain control and symptom removal to be held at the Sheraton Hotel, October 3, in conjunction with the annual meeting of the Society for Clinical and Experimental Hypnosis. For further information, write to: Dr. Arthur H. Wald, Institute for Research in Hypnosis, 33 East 65th Street, New York 21.

U. S. Public Health Service Hospital, Carville, Louisiana: A 19 minute, 16 mm. sound and color film on the management of the leprosy patient is available for loan or purchase. To obtain the film on loan, write to: Communicable Disease Center, Atlanta 22, Attention: Audiovisual. To purchase the film, write to: United World Films, Inc., 1445 Park Avenue, New York 29.

World Forum on Syphilis and Other Treponematoses, Washington, D. C.: Sponsored by the United States Public Health Service and other official agencies and voluntary organizations, this meeting will be held September 4-8, 1962, at the Sheraton Park Hotel. It will immediately precede the meeting of the International Congress of Dermatology, to be held September 9-16 at the Shoreham Hotel. For further information, write to: Dr. William J. Brown, Chairman, Program Committee, Venereal Disease Branch, Communicable Disease Center, Atlanta 22.

Acute Arterial Injuries

OSCAR CREECH, JR.*

Tulane University School of Medicine, New Orleans

THE progress that has been made in the treatment of arterial injuries closely parallels the progress made in treatment of other cardiovascular conditions. As background to my remarks, I would like to present an account of the first successful repair of an arterial injury, in 1759 at Newcastle upon Tyne, England, by a Mr. Hallowell. I am embarrassed to tell you that the operation was suggested to Mr. Hallowell by his associate, a *physician* named Lambert, who reported the case.

"The case of the aneurysm was indeed curious, and I am in hopes will prove useful, but I am not too sanguine in its favor till I have seen the effects of such an operation confirmed by several instances. Till then I would not be fond of saying anything of it in print except that as few of these inquiries may fall to any single man's share in the ordinary case of business, it will, by that means, afford a larger field to put evidence upon the trial so as to introduce the methods sooner. If this be your opinion I have no objection to your giving any short account of it you may think proper."

In this letter to John Hunter, Dr. Lambert wrote further: "I have very carefully attended to the cure of three aneurysms for which the operation was performed by my late, worthy friend and colleague, Mr. Hallowell. In one of them, after the operation was performed in the common way by ligature above and below the aperture in the artery, such violent pain, swelling and inflammation came on as to threaten a gangrene. Bleeding, fomentation, poultices, and so forth mitigated these symptoms. A plentiful suppuration resulted. The wound gradually healed and the patient was then discharged from the hospital with a weak arm and a pulse much weaker in [one] wrist than in the other. This case in particular made me turn my mind to the operation for the aneurysm and made me wish to see it done with some alteration in the method so as to make less disturbance in the circulation of the part. I recollected all I had seen or read of the styptics, of pressure, of ligatures, and of the cure of hemorrhages. I considered the coats and motions of the arteries and compared their wounds with the wounds of veins and other parts. I reflected upon the process of nature in the cure of wounds in general and considered in particular how the union of the parts was brought about in the operation of a harelip and in horses' necks that are bled by farriers."

The technic that Ambroise Paré introduced to treat harelip is shown in figure 1. A short steel pin is introduced through the margins

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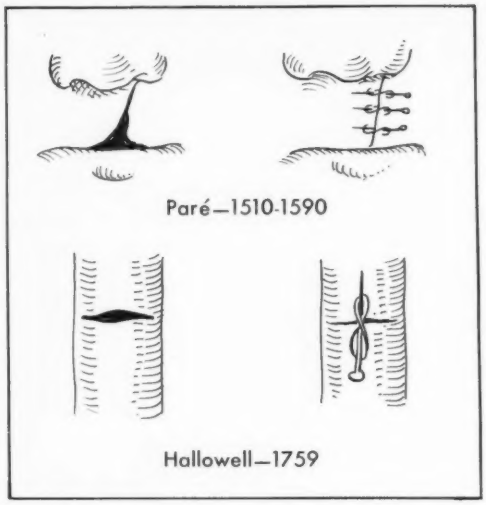

FIGURE 1. The method of repairing harelip as described by Ambroise Paré was employed in the first arterial repair. A small steel pin was inserted through the margins of the wound and a thread wound around it in figure-of-eight fashion to bring the edges of the wound together.

of the lip and then the margins are brought together by wrapping a figure-of-eight suture around the pin. This was the technic Lambert suggested to Hallowell for treating an injury of the brachial artery. His letter to Hunter continued:

"Upon the whole I was in hopes that a suture of the wound might be successful and, if so, it would certainly be preferable to tying up the trunk of the vessel. I communicated my thoughts to Mr. Hallowell, Mr. Keenlyside and some other friends of the profession. A case of aneurysm from bleeding occurred and fell to Mr. Hallowell's lot. I recommended the method that I had hinted, and he put it into execution June 15, 1759. Everything was done in the usual method till the artery was laid bare and its wound discovered, and the tourniquet now being slackened, a gush of blood per saltum showed there was no deception. Next, two ligatures, one above the orifice and one below, were passed under the artery that they might be ready to be tied at any time if the method proposed should fail. Then a small steel pin, rather more than a quarter of an inch long, was passed through the two lips of the wound in the artery and secured by twisting a thread around it, as in the harelip. [Figure 1.] This was found to stop the bleeding, upon which the arm was bound up, the patient put to bed in order to be kept quiet, as is usual in such cases. The wound was first dressed on the fourth day, that is June the 18th, and it looked well for the time and continued to heal without interruption in a timely manner.

"If it should be found by experience that a large artery when wounded may be healed up by this kind of suture without becoming impervious, it would be an important discovery in surgery. It would make the operation for the aneurysm still more successful in the arm when the main trunk is wounded, and by this method perhaps we might be able to cure the wounds of some arteries that would otherwise require amputation or be altogether incurable."

This report apparently received attention, but no one attempted to repeat the method until 1773 when Assman used it in some experiments. He made wounds in the femoral arteries of dogs and closed them in the manner described, and none of the experiments were successful. These results led Assman to describe the method as insecure and dangerous, and he concluded further that injury of blood vessels is followed immediately by thrombosis and that repair could not take place in an artery without the lumen being obliterated by a clot. This erroneous conclusion was responsible for lack of interest in direct surgical repair of acute arterial injuries for more than a hundred years.

Late in the nineteenth century, interest again was expressed in this problem. It was found that with proper sutures of linen or flax, which were oiled, and with fine needles one could close lateral wounds in arteries. In fact, there were a number of case reports of successful suture of lateral arterial wounds in man.

The first successful repair of a complete arterial injury, i.e., complete severance of an artery, was accomplished by John B. Murphy in 1897. It was a gunshot wound of a femoral artery, and he made an anastomosis not by the methods we use today but by invaginating

the upper end into the lower. Murphy thought this was the proper way to achieve a good union. The patient survived and had a good pulse in the injured extremity.

About the turn of the nineteenth century surgeons became interested in improving the technics of vascular repair. You are familiar with the many contributions of Guthrie and Carrel to the technics of arterial suture. When World War I began, it appeared to offer an opportunity for the use of these methods in repair of arterial wounds on the battlefield. A number of surgeons went to France prepared to treat arterial wounds by immediate suture. However, Machins expressed the belief that in the light of present knowledge the repair of arterial wounds on the battlefield was not feasible. He was prophetic in this conclusion, because there were almost no instances of successful arterial suture in World War I. In fact, in World War II there were only 80 instances in which arteries were repaired and not all of these were successful.

During the Korean War the reparative treatment of acute arterial injuries became a reality. By this time a great deal had been learned from operations for patent ductus and coarctation. Thus, it was demonstrated that immediate repair of acute arterial injuries was feasible even under the difficult conditions imposed by military combat. Subsequently, these methods have been applied to the treatment of injuries encountered in civilian practice and have proved not only feasible but highly successful.

The frequency of arterial injury is probably greater than reports in the literature imply. This is because many arteries which are injured are not of major caliber and thus interference with blood flow goes unrecognized. Further, some arteries that are considered vital are not necessarily so, since under certain circumstances they can be acutely occluded without producing the manifestations of ischemia. Thus, if the situation at the moment of occlusion is such that adequate collateral circulation can and does develop, there may be only transient or no ischemia although a major vessel is interrupted. Finally, lateral wounds of large arteries may be temporarily sealed by hematoma formation, and the injury may become evident only after an aneurysm or an arteriovenous fistula is demonstrable. If one makes a practice of performing arteriograms in penetrating wounds involving the extremities and in dislocations and fractures of major long bones, the frequency of arterial involvement will be apparent.

Types of Injury

Pathologically, arterial injury may consist of laceration, spasm, complete severance or contusion (figure 2). Laceration is probably the most common type and may consist of a clean, incised wound as in a knife stab or may be ragged as in the case of a gunshot wound. In any case, the lacerated wound is most often a lateral wound involving only a portion of the circumference of the artery. For this reason the natural hemostatic mechanisms are not completely effective and bleeding is much more severe in this type of injury than in other types.

Arterial spasm is not fully understood. Anyone who has exposed and manipulated an artery has observed that the slightest traction on the vessel results in significant reduction in its diameter. This is intrinsic arterial spasm, since complete denervation may not prevent or relieve it. Even vessels as large as the common femoral artery may effect a reduction in their diameter of 50 per cent as a result of stretching. Spasm may be so severe at times that serious ischemia of the tissues will result, and unless spasm is relieved actual necrosis may ensue.

Rarely is complete severance of an artery accomplished by a sharp instrument; rather it is most often a result of crushing injury, a high-velocity missile or a bone fragment. For this reason the ends are ragged, the adventitia is frequently not completely divided, and the formation of clot within the lumen and immediately outside the vessel is common. Thus, the completely severed artery rarely is associated with severe hemorrhage.

Contusion of an artery commonly results from the vessel being caught between two opposing forces. Formerly it was believed that contusion resulted simply in intraluminal thrombosis, but with experience it has become

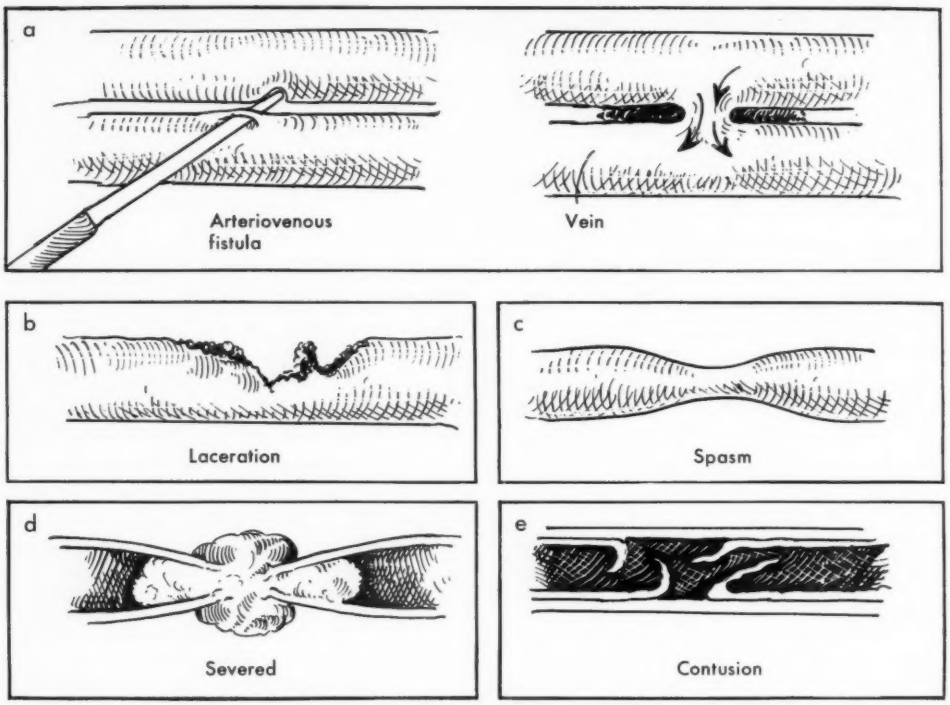

FIGURE 2. Types of arterial wounds. In the development of an arteriovenous fistula there is injury to adjacent walls of artery and vein with the result that a communication develops between them.

evident that this is rarely the case. Usually, a contusion results in direct damage to the intimal coat and sometimes to the medial coat. The simplest injury is longitudinal striations of the intima producing thrombosis without any direct break in the lining of the blood vessel. The next most common type is that in which the intima and part of the media are completely disrupted and roll back on themselves like a scroll. When the column of blood strikes this area it produces dissection and complete occlusion.

Arteriovenous fistula is one of the most common sequelae of arterial injury, and the way in which the communication between artery and vein is produced is indicated in figure 2a. The most trivial lateral wounds can result in this condition, and since the wound may not significantly interfere with blood flow to parts distal to the injury, it is often overlooked.

In a series of 116 cases of acute arterial injury observed at the Baylor University Hospitals, complete severance of an artery was most common, then laceration, contusion and spasm, in that order (table 1). Wounds of the brachial artery were most frequent, followed in order by involvement of the femoral, radial and ulnar, and carotid arteries and the thoracic aorta (figure 3).

Since arterial injuries often involve pe-

TABLE 1

TYPES OF WOUND IN 116 CASES OF ACUTE ARTERIAL INJURY

WOUND	NUMBER OF CASES
Laceration	43
Severance	66
Contusion	5
Spasm	2
	116

ripheral vessels, they commonly occur in association with trauma to other structures. Injury to adjacent nerves, veins and tendons were most commonly associated with arterial injuries in this series (table 2). Fracture of the bone adjacent to these injuries was also encountered frequently.

Diagnosis

A history of the loss of a large quantity of blood is important to the diagnosis of acute arterial injury. By the time the patient reaches the emergency room his wound may not be bleeding, but on questioning one finds that immediately after injury a large hemorrhage occurred. It makes no difference whether the blood lost was dark or red or whether it had a pulsatile character. The occurrence of significant blood loss is sufficient indication for complete examination to determine the presence of arterial injury.

In examining the patient, certain signs may be helpful. Classically, acute occlusion of an artery is followed by pain, pallor, pulselessness and paralysis of the involved part (table 3). It should be emphasized that these cardinal signs are present only if a major artery is completely interrupted, and even then they may be temporary only. In our experience pain is not common. In fact the patient more often complains of numbness in the presence of severe ischemia. Pallor may be present, but often by the time the patient has reached the physician collateral blood flow has become established and color may have been restored. Thus, pallor is not a reliable sign. Absence of pulses clearly points to interruption of arterial continuity, but the presence of pulses does not exclude injury provided there is evidence of a penetrating wound adjacent to a major arterial trunk. Paralysis is relatively uncommon, and anesthesia of the part is evident much earlier. This is because sensory nerves are more sensitive to ischemia than motor nerves.

The clinical diagnosis of acute arterial injury is based largely on suspicion aroused by a history of severe bleeding at the time of injury, the presence of a large hematoma, and the signs of transient ischemia (table 4). To reiterate, if the patient has a pallid, cold, pulseless foot, it is perfectly obvious that something important has happened to the arterial system above. On the other hand, if the patient has a faint pulse, good color to the foot, and no real evidence of ischemia, one must

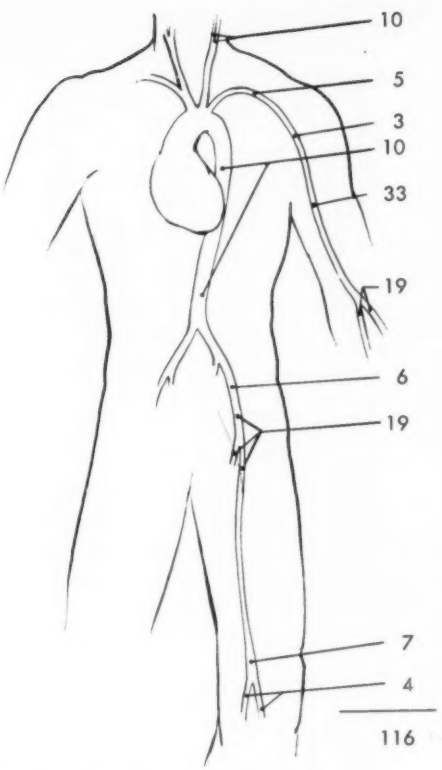

FIGURE 3. Locations of 116 arterial injuries.

TABLE 2

ASSOCIATED INJURIES IN 74 CASES OF ARTERIAL INJURY

ASSOCIATED INJURY	NUMBER OF CASES
Extensive soft-tissue injury	3
Fracture of adjacent bone	10
Fracture of other bones	6
Dislocation of adjacent joint	1
Injury of adjacent nerves	29
Injury of adjacent tendons	16
Abdominal injury	10
Chest injury	6
Injury to major veins	17
Other injuries	3
	101

TABLE 3

SIGNS IN DIAGNOSIS OF ACUTE ARTERIAL INJURY

Pain
Pallor
Pulselessness
Paralysis

TABLE 4

CLINICAL DIAGNOSIS OF ACUTE ARTERIAL INJURY

Suspect when there is:
Severe bleeding
Large hematoma
Transient ischemia

look further to determine the presence of arterial injury. Transient ischemia is one of the most important signs, and the fact that it is present such a short time when there is a wound of a major peripheral artery merely indicates the rapidity with which collateral circulation begins.

Arteriography

One can suspect arterial injury from clinical manifestations alone, but diagnosis can be established beyond doubt by arteriography. We employ roentgenographic examination in every case where arterial injury is suspected and, in fact, use it on many occasions when there is injury of an extremity without any evidence of arterial damage. The procedure is carried out under local anesthesia. A No. 18 spinal needle is inserted percutaneously into the vessel and well above the external wound or the fracture site. Fifteen cubic centimeters of 50 per cent HYPAQUE® is injected rapidly and an exposure is made near the end of the injection. This technic can be employed for visualization of any of the peripheral arteries, but for aortography different technics are employed depending on the level of the suspected injury.

The value of arteriography is demonstrated by the following case. A man sustained a gunshot wound in the middle third of the thigh and was brought to the hospital immediately. There were no pulses in the foot and the extremity was pallid. The resident suspected an arterial injury and planned to obtain an arteriogram, but within a few minutes the patient's foot became warm and pink and the pulses returned, suggesting transient spasm. One of the staff was consulted, and in view of the history of transient ischemia he suggested that an arteriogram be obtained. It revealed extravasation at the site of the arterial wound (figure 4). If this roentgenogram had not been made, the diagnosis of an arterial injury would not have been made and, as demonstrated at operation, the communication between the femoral artery and vein would have become clinically evident as an arteriovenous fistula weeks or months later. In discussing this problem with a visitor recently, I was asked if we encountered many arteriovenous fistulas. I replied, "No, because we prevent them; we treat the acute injuries when they occur." The proper approach, then, is to confirm or exclude the possibility of arterial injury by arteriography.

Arteriography may be especially helpful in the presence of fractures. In a recent case there were fractures of the tibia and fibula and the patient had evidence of severe ischemia in the foot. It was not clear whether the arteries were occluded, torn apart, or simply compressed between the fragments. Arteriography revealed that the anterior and posterior tibial arteries were intact until they reached the fracture site, where there was extravasation of dye indicating complete disruption of these vessels. Because of the extensive loss of substance and the small size of these arteries, anastomosis was impractical and amputation was necessary.

Treatment

Once the diagnosis has been established, the decision must be made to operate at an appropriate time. Much has been said about the interval between injury and treatment. Several years ago the critical time was placed at eight hours; then it was increased to 12 hours, and during the Korean War it was raised to 18 hours. As a result of our experience I do not believe there is an interval between injury and treatment which precludes success. To be sure, if a patient is seen by the physician 10 min-

utes after injury and undergoes operative repair in another 10 minutes, his chances are excellent to have a patent vessel and normal blood flow. However, success or failure depends on whether the patient has a patent distal arterial tree. For example, we have treated patients with injury of the common femoral artery who were brought to the hospital within 15 minutes, whose blood volume was promptly replaced and who were operated on within an hour, yet there was complete thrombosis of the entire arterial system distal to the injury so that restoration of blood flow was impossible. In fact, irrespective of the time interval, the cause of failure to re-establish blood flow is more often occlusion of the arterial tree distal to the injury than faulty repair.

The cause of intravascular thrombosis following arterial injury is probably the sudden depletion in blood volume with a reduction in blood pressure below a point which is adequate to maintain an effective collateral blood flow. There is convincing evidence that the collateral channels in any part of the body are adequate to sustain the viability of distal tissues if the occlusion is appropriately placed to take advantage of collaterals and if an adequate blood flow and perfusing pressure can be maintained. Restoration of blood volume with maintenance of a relatively normal blood pressure, therefore, is more important than the interval between injury and treatment. Thus, when a patient is admitted to the emergency room and an arterial injury is suspected, we attempt to replace blood volume as rapidly as possible so that collaterals can begin to function immediately (table 5). When these preliminary steps have been taken it has been possible to successfully repair arterial wounds as long as 72 hours after injury.

The necessity for the control of hemorrhage from an injured artery requires little comment. This can be accomplished usually by means of simple pressure over the external wound, and only when hemorrhage persists should one resort to a tourniquet. One should move the patient to the operating room if exploration of the wound is necessary to control bleeding.

FIGURE 4. Arteriogram made soon after a gunshot wound of the thigh. Extravasation of contrast material from the superficial femoral artery in its middle third. At operation a wound of this artery was discovered and successfully repaired.

Since arterial injuries are often associated with injury to other parts, priority for treatment of the various injuries is a matter of clinical judgment and need not be discussed at this time.

Prior to repair of an arterial wound it is necessary to expose the vessel above and below and apply occluding clamps or tourniquets in order to control bleeding during dissection and repair. When a large hematoma is present in a wound of an extremity, an external tourniquet can be applied about the extremity proximal to the wound until the site of arterial injury has been exposed. Then occluding tapes

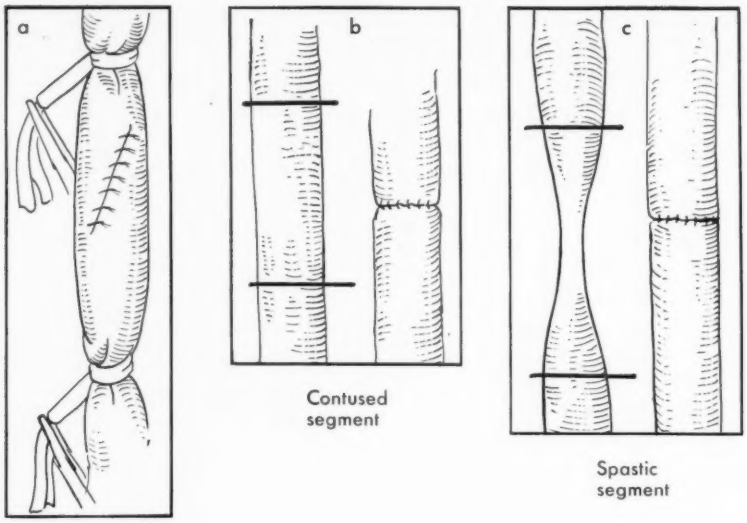

FIGURE 5. Prior to repair of a wounded artery the vessel should be controlled above and below the wound, with occluding clamps or tourniquets. Lateral wounds are closed by simple, interrupted or a continuous suture. A contused segment of artery usually is treated best by excision and end-to-end anastomosis.

Arterial spasm may be overcome by occluding the vessel above and below the spastic segment and injecting saline under pressure. If this fails, resection and end-to-end anastomosis should be performed.

can be applied directly about the artery above and below the wound to facilitate mobilization of the vessel and to remove tension on the suture line during anastomosis.

When an arterial wound has been exposed, occlusion should be released alternately above and below the wound in order to insure a free flow of blood from both segments of the vessel. This is one of the most important steps in assuring success of a restorative operation. In wounds at almost any level there should be brisk bleeding from the distal arterial segment when the occluding device is released. If this is not the case, one should suspect that acute thrombosis has occurred and an attempt should be made to remove thrombi by massaging the tissues distal to the wound, in the case of injury of a peripheral artery, by introducing a catheter into the distal segment of the vessel and applying gentle suction, or, when other measures have failed, inserting a plastic catheter into a small terminal branch and irrigating the artery with physiologic saline solution. In most instances these maneuvers will remove clots from the distal arterial segment and will restore patency to the vessel.

In the management of the arterial wound itself, it is important to make sure that uninjured arterial wall is repaired or anastomosed (figure 5). In some instances of gunshot wounds the gross injury to the arterial wall is relatively limited; however, microscopically, the damage can be shown to extend for 0.5 to 1.0 cm. on either side of the wound. Thus, careful debridement is necessary before beginning repair. In the case of contused wounds the artery should be transected and the lumen examined carefully for disruption of the intima and for dissection. It is usually necessary to resect the contused segment to avoid intimal dislocation and dissection after continuity has been restored.

In carrying out end-to-end anastomosis an arterial graft is rarely necessary, since by mobilizing the vessel for a considerable dis-

TABLE 5

TREATMENT OF ACUTE ARTERIAL INJURY

Restore	Blood volume
	Arterial continuity
Repair	Associated injuries

TABLE 6

TREATMENT OF ARTERIAL INJURY ASSOCIATED WITH INJURY TO SKELETAL STRUCTURES

Attempt manipulation only once.
Open operation.
Restoration of blood volume.
Fixation of fractures.

tance above and below the injury and by flexion of the extremity, when the injury occurs in the region of a joint, the ends can be approximated without difficulty in most cases. If a graft is necessary one may use a segment of the internal saphenous vein or a synthetic graft. Where arterial replacement is necessary in the region of a joint the former is preferable.

Severe arterial spasm usually can be overcome by occluding the vessel above and below the spastic area and injecting physiologic saline into the occluded segment. When this is not effective one should not hesitate to divide the artery in the center of the spastic zone and to stretch the vessel with a hemostat.

Rarely, an arterial injury is associated with severe loss of surrounding soft tissues so that there is little remaining to cover the vessel after repair. In our experience the synthetic prostheses have functioned well under these circumstances since they do not need surrounding soft tissues for survival. In fact, it has been observed that the synthetic graft will function satisfactorily although completely exposed for long periods. For example, a schoolboy was injured in a hunting accident and sustained a shotgun wound of the thigh with a compound fracture of the femur, loss of most of the muscles on the anterior surface of the upper third of the thigh and groin, and loss of about 6 in. of the femoral artery. A synthetic graft was employed to restore arterial continuity, but there was no soft tissue available to cover the graft. It was left exposed and functioned well with normal vascularity of the distal extremity. As granulations developed, epithelial covering of the wound commenced. In about three months most of the open area had been covered but a residual portion of the graft was still exposed. We attempted to cover it surgically by using a pedicle from the medial surface, but in about 10 days the graft had protruded from the edge of the pedicle. A large portion of muscle was then shifted to cover it and again the graft worked its way to the outside. It then became apparent that the graft was resisting efforts to cover it because it was a foreign body in an infected wound. After about five months, bleeding began to occur from the proximal anastomosis so the graft was removed. By this time, however, the soft tissues had regenerated enough so that there were adequate collateral channels to support the extremity. Today the boy has a useful limb. Thus, whenever the situation is such that the blood vessel replacement cannot be covered, one should use synthetic materials rather than venous or arterial grafts.

FIGURE 6. Arteriogram three days following dislocation of the knee and the development of ischemia in the foot and leg. There is complete occlusion of the popliteal artery, which led to amputation of the extremity.

FIGURE 7. a. Arteriogram shortly after dislocation of the knee. Complete occlusion of the popliteal artery.

b. Immediate operation with resection of the contused segment and end-to-end anastomosis resulted in restoration of normal patency of the vessel.

Treatment may be more difficult when arterial injury is associated with injury to skeletal structures. The orthopedists see many of these patients first and thus it is their opportunity to treat or mistreat them first. More than any other group, the orthopedists should appreciate the significance of early and often transient signs of arterial insufficiency. It should be a policy that when a patient has a fracture and there is any evidence of ischemia, such as transient pallor or transient alteration in pulses, one should consider the possibility of arterial injury. Manipulation is attempted only once and if, following this, the distal pulses are good and the limb has evidence of an adequate blood supply, treatment of the fracture is continued (table 6). On the other hand, if manipulation fails, if the signs of ischemia are not completely relieved, or if there is any doubt in the mind of the surgeon about the adequacy of arterial supply, an arteriogram should be obtained.

Dislocations of the knee and elbow are often associated with arterial injury. For example, a young man sustained a dislocation of the knee during a football game. He was seen by a physician immediately. The dislocation was manipulated and reduced in the conventional fashion, although it was observed at the time that the patient had no distal pulse and there was evidence of ischemia. Almost three days later when irreversible soft-tissue changes had occurred, an arteriogram was made which revealed complete occlusion of the popliteal artery (figure 6). By this time ischemic changes in the muscles were so advanced that repair was not feasible and amputation had to be done. This emphasizes the tragic consequences of failure to appreciate the significance of early signs of ischemia following skeletal injury.

On the other hand, when the presence of arterial injury is recognized early and treatment instituted promptly the results are grati-

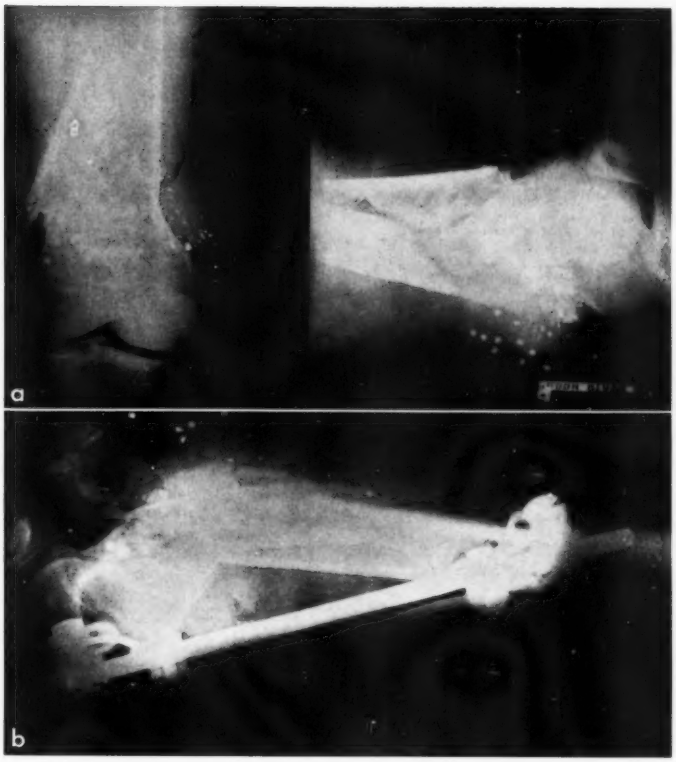

FIGURE 8. a. A shotgun wound of the lower third of the thigh produced destruction of the superficial femoral artery.

b. At operation the artery was repaired and the fracture immobilized. Eight days later the immobilizing apparatus failed: acute angulation of the fragments and disruption of arterial repair occurred.

fying. In another instance of dislocation of the knee the presence of arterial injury was suspected early and an arteriogram confirmed the diagnosis of occlusion of the popliteal artery (figure 7). Immediate operation was carried out, a thrombosed segment of the vessel was resected, and the popliteal artery was anastomosed. These procedures resulted in restoration of the blood flow.

When arterial injury is adjacent to a fracture it is essential to immobilize the extremity completely in order for healing of the arterial wound to take place. As an example, a man received a shotgun wound in a hunting accident which produced a severe comminuted fracture of the lower end of the femur with the loss of about 2 in. of the femoral artery. The artery was repaired and the fracture was reduced, but on the seventh day the immobilization gave way and the arterial anastomosis was disrupted (figure 8).

There are times when the physician makes a diagnosis of an acute arterial injury but is not in a position to carry out definitive therapy. Under these circumstances he should attempt to control bleeding by compression. If this is not possible the patient can be moved to the operating room, the arterial injury exposed, and the vessel immediately above and below ligated. If this is done, the ends of the ligatures should be left in the subcutaneous tissues to facilitate mobilization of the vessel when repair is attempted. The blood volume should then be restored and the patient moved to a place where the facilities and personnel will permit repair of the injury.

I know of no other injury in which an aggressive attitude in treatment is more rewarding. In most instances one is not attempting to save a life but a limb, and adherence to a few simple principles is all that is necessary to achieve successful results.

Some Problems of Thermal Injury

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I SHALL not attempt to discuss comprehensively the many problems that seriously burned patients face. Rather, I will direct attention to a few of the problems which are currently attracting interest among clinical and laboratory investigators.

Burn Shock

From the practical point of view, the primary measure in prevention of shock from burns is replacement of fluid loss. There is no question that shock resulting from burns is caused primarily by the rapid loss of fluid from the blood stream, which decreases the volume of circulating blood. Direct injury of the blood vessels in the burned areas increases the permeability of the capillary walls, and fluid either accumulates in the subcutaneous tissue if the burn is deep or is lost from the surface if the burn is superficial. Fluid loss begins almost immediately after injury and reaches a peak in the first several hours. The rate of fluid loss declines after 6 to 12 hours,

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and after 24 hours the tide begins to turn; fluid comes back from the tissues into the blood stream, and the most critical period of shock is over. Burn shock is principally a problem of the first 24 hours after injury, and almost never is a problem after 36 hours.

The immediate response to the mildest burn is a brief period of vasoconstriction followed by dilatation of the capillaries, the finer arterioles and the venules, with greatly increased blood flow. A somewhat more severe injury increases capillary permeability locally, and plasmalike fluid leaks into or out of the tissue. The electrolytic pattern of the fluid is similar to that of plasma; its protein content is lower, but with a higher proportion of albumin. At the same time, there is an abnormal exchange of certain constituents between the extracellular and intracellular fluids (sodium, potassium, certain proteolytic enzymes). Present evidence indicates no generalized loss of fluid in unburned regions. A certain number of red blood cells in the capil-

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laries may be damaged; sludging and thrombosis may occur.

Millican[1] has shown that in tourniquet injury, edema-fluid sodium is rapidly exchangeable with that of the plasma. Presumably this is true of other electrolytes and water. The protein is only slowly exchangeable.

The tissue space becomes distended with fluid from leaking capillaries. If this fluid is near the surface, blisters form which eventually rupture. Capillary leakage at deeper levels results in local edema; some fluid finds its way into the lymphatic system, giving rise to greatly increased lymph flow from the burned area. The tissue cells and intercellular substances, such as collagen, are denatured and injured to varying degrees, depending on the intensity and duration of the burn. A full-blown inflammatory reaction with the usual leukocytic response sets in.

Estimate of Extent of Injury

The extent of injury to a burned tissue depends on the intensity, quality and duration of the thermal stimulus. The effects range from the simple reversible dilatation and superficial cellular damage characteristic of superficial burns to a marked increase of capillary permeability, thromboses, and extensive cellular destruction characteristic of deep burns. Burns are generally classified according to their depth into three categories: first-degree, simple erythema; second-degree, partial destruction of the skin but without the destruction of all the deep epithelial cells; third-degree, the destruction of the full thickness of the skin.

The severity of a burn depends not only on its depth but also on its extent. The diagrams for charting burned areas based on these measurements and related information (figure 1) are reproduced from an article by Lund and Browder.[2] The "rule of 9s" was introduced recently to make possible an even quicker estimation in event of mass disaster (figure 2). This method provides a roughly correct estimate for an adult or older child but a poor approximation for an infant.

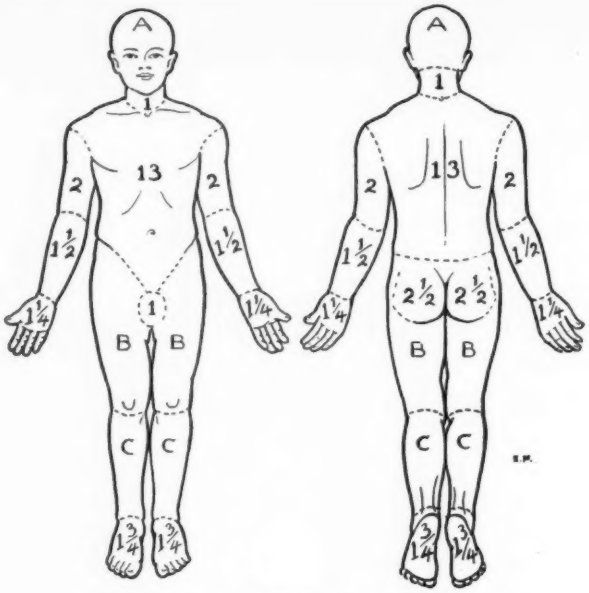
Responses of different persons to burns of apparently equal depth and extent may vary considerably, depending in part on their age and prior state of health. Mortality is disproportionately high among infants and elderly and infirm persons.

The amount of fluid leaking into or from a burned area depends on the extent of the area, the vascularity of the tissue, and the depth of the burn. There is no evidence that the adrenocortical hormones influence permeability of the damaged capillaries or the resultant fluid loss. Resorption of the edema fluid, which begins after about 36 to 48 hours, proceeds slowly and usually takes from five to seven days.

The amount of fluid loss and reduction in blood volume usually is indicated by a rising hematocrit, hemoglobin and red blood cell count. However, the apparent hemoconcentration may not parallel the oligemia, because (1) measurements of hematocrit and hemoglobin in samples obtained from peripheral vessels may not reflect the true "body" values, and (2) hematocrit determinations will also be misleading if extensive red cell lysis has occurred or if the patients were anemic or, rarely, polycythemic prior to being burned. A rapid exchange of fluid may be taking place about 24 hours after injury without much change in hematocrit; return of fluid to the vascular bed may keep pace with the loss. This will be shown by a progressive fall in plasma protein concentration, since the concentration of protein in the returning extravascular fluid is lower than it is in plasma.

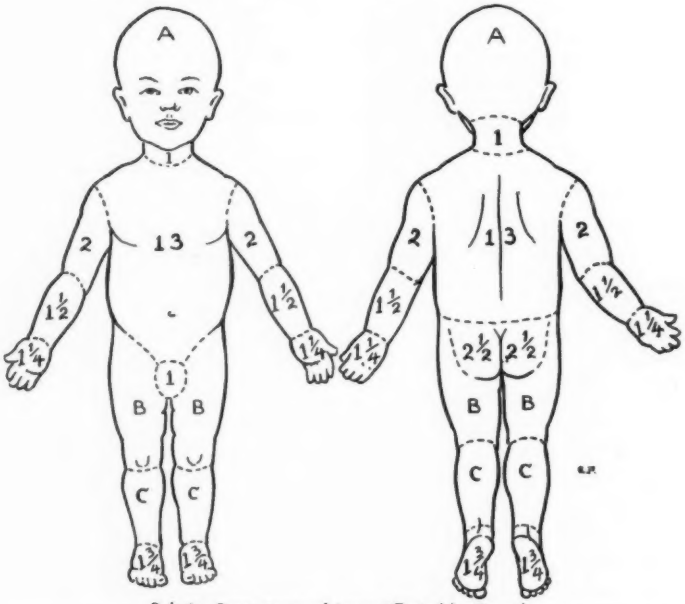
Hemoglobinemia and hemoglobinuria are maximal soon after the burn and then subside gradually during the first 24 to 72 hours. The red cell pigments in the plasma and urine are generally oxyhemoglobin mixed with traces of methemoglobin.

Hemoglobinemia is caused by destruction of red cells, a process which occurs only in association with deep burns. A superficial burn, no matter how extensive, does not produce hemoglobinemia, and hence this sign indicates a fairly extensive area of deep burn. The blood of severely burned patients may show early alterations from the heat, varying from only slight spherocytosis of erythrocytes to advanced spherocytosis and fragmentation.



Relative Percentages of Areas Affected by Growth

Area	Age 10	15	Adult
A = ½ of head	5½	4½	3½
B = ½ of one thigh	4¼	4½	4¾
C = ½ of one leg	3	3¼	3½



Relative Percentages of Areas Affected by Growth

Area	Age 0	1	5
A = ½ of head	9½	8½	6½
B = ½ of one thigh	2¾	3¼	4
C = ½ of one leg	2½	2½	2¾

FIGURE 1. (From Lund and Browder.[2])

There may be a considerable increase in osmotic fragility. Studies of the mechanism of these changes in red blood cells have revealed no cold or warm agglutinins or hemolysins. Shen, Ham and Fleming[3] concluded that the destruction of a considerable volume of erythrocytes may result from heating of blood at the site of the burn, depending on at least three major factors: temperature attained by the blood, duration of heating, and volume of blood subjected to these conditions. The actual number of red cells involved in this process is rarely more than 10 to 20 per cent of the circulating erythrocytes.

The serum sodium concentration generally is on the low side early after severe burns, as are the serum chloride and protein concentrations, particularly albumin, which, being smaller than the globulins, moves across the capillary membrane faster. It is unusual to find an increase in potassium concentration in the serum of a burned patient great enough to constitute a toxic hazard.

Anticipation and Prevention of Burn Shock

A burned patient in fully developed shock is apathetic, chilly, often nauseated, pale and cyanotic. Blood pressure is low, and pulse is rapid and thready. Cardiac output is low, peripheral resistance is high, peripheral blood flow is decreased, and urinary output is low. The diagnosis of burn shock at this stage is easy, but to wait for this stage to appear is analogous to waiting for the appearance of a cavity in the lung before making the diagnosis of pulmonary tuberculosis. If shock persists, irreversible changes in the function and structure of vital organs may result. Therefore, the problem must be attacked by preventing shock.

Shock may be anticipated in a previously healthy adult with a burned area of 15 per cent or greater. In elderly or very young persons, a burned area of as little as 8 per cent may lead to circulatory failure if untreated. Any procedure that may increase shock (e.g., dressings) should be avoided or postponed until shock has been prevented or treated. Restoration and maintenance of blood volume are vital.

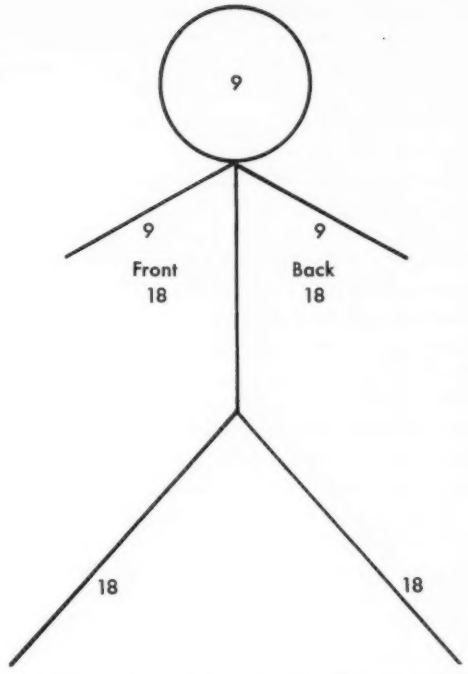


FIGURE 2. The "rule of 9s" for estimating area of skin surface burned.

Replacement of Fluids

At present, replacement therapy usually is undertaken with a combination of whole blood, electrolyte solutions and a colloid-containing fluid. The widest experience with plasma expanders has been with dextran, and it has proved generally satisfactory. The bleeding tendency that has been observed when dextran has been infused in moderate amounts into normal volunteers has not been reported in burned patients receiving large amounts of dextran in the first two days after injury, nor have immunologic reactions proved to be a problem. Human serum albumin is possibly preferable to the plasma expanders but is not generally available in adequate quantities. If safe plasma (free of hepatitis virus) is available, it is a desirable material to use in the treatment or prevention of burn shock.

A definite answer is not yet available regarding the advisability of using whole blood

for replacement therapy in the burned patient. The experimental evidence favoring its use was first presented about 15 years ago, but the clinical evidence certainly is not conclusive, since properly controlled studies with patients have not been made. There is also some recent experimental evidence suggesting that whole blood may be detrimental to burned dogs. Investigators at Southwestern University[4] treated burned dogs with saline or with an equal volume of saline and whole blood and reported a higher mortality rate among the animals receiving whole blood. At autopsy they found severe pulmonary congestion in the animals which received whole blood but not in those given saline alone. These workers felt that giving whole blood leads to pulmonary congestion, to interference with aeration and oxygenation of blood, and to death from hypoxia. Again, appropriate studies with patients have not been made to determine the effects of whole blood in prevention or treatment of burn shock. However, there seems little justification at present for its use.

For a patient whose burns are not too extensive and who is seen relatively early, there is evidence that a mixture of sodium chloride and sodium bicarbonate in water by mouth is adequate treatment. Rosenthal[5] and co-workers and Markley and associates[6] revived interest in the use of sodium chloride solution alone or with other sodium salts. They showed that the therapeutic effects of sodium salts given to rodents and man intraperitoneally, orally or intravenously after burns are similar to those of serum or plasma. In some experiments the effect of serum appeared to be due not to its protein but to the sodium, while in other experiments when the fluids were administered to mice in divided doses both serum and dextran gave better therapeutic responses than equivalent amounts of saline, when less than full therapeutic amounts of either were given. The therapeutic effect of the sodium salt was shown to be due to the sodium cation rather than to its anion, since different sodium salts yielded similar results. Isotonic saline solution was more effective than the hypertonic solution. The mortality rate was increased when potassium salts were given.

Patients with burns covering about 25 per cent of the body surface generally can be handled well using saline orally. The amounts required, timing, etc. have been described by Markley and associates.[6] Patients with more extensive burns may be vomiting or may be in shock, and parenteral therapy is then indicated, rather than oral fluids. In addition, of course, glucose and water must be given to provide for insensible loss and for some urinary excretion.

The use of urea and other osmotic diuretics is currently being considered as a treatment for burned patients. There is evidence based on studies of animals[7] and also at least one series of patients, reported by Schilling and co-workers[8] from Oklahoma, that administration of urea seemingly results in more effective shock therapy. The rationale for giving urea is that it is a relatively nonmetabolizable substance and it crosses cell membranes and diffuses into all body water. It is excreted by the kidney and carries with it water, producing an obligatory osmotic diuresis. Evidence presented by Schlegel[7] suggests that one may be able to handle the electrolyte and fluid problems of the patient a bit more easily if urea is added to the parenteral fluid, but it probably will be another year or two before we know definitely whether or not this form of therapy has significant value. Also, work is going on to see if other substances, such as mannitol, may have properties equal or superior to urea for this purpose.

Many factors must determine the amount and rate of fluid, colloid and electrolyte replacement. The extent, location and depth of the burn and the age, weight and prior health of the patient are the most important. We have found the clinical appearance of the patient, the degree of hemoconcentration, and the urinary output to be useful therapeutic guides. All patients with extensive burns should be provided with constant bladder drainage immediately, and an accurate hour-to-hour record of urinary output should be kept during the first 24 to 48 hours. Renal blood flow and urinary output may be greatly reduced at a time when the peripheral pulse and blood pressure are normal and before

other definite signs of impending shock are seen. When the output of urine is good, one may feel sure that the general circulation is good, but if urinary output falls, one must anticipate early failure of general circulation.

Since the greatest fluid loss occurs in the first few hours, it is during this time that the physician has the best opportunity to prevent shock. Fluid therapy should be started at once for seriously burned patients. It seems that most patients with burns involving up to 20 to 25 per cent of the body surface can be treated satisfactorily with a sodium chloride-sodium bicarbonate (or citrate) mixture if treatment is started early. Often this mixture can be given orally, in concentrations of 75 mEq. sodium and 50 mEq. chloride per liter. However, if the patient is in shock or is nauseated, oral fluids alone are inadequate and intravenous fluids should be started, since gastrointestinal function may be impaired. When the usual peripheral veins are not available, there should be no hesitation about cannulating a vein, using a polyethylene cannula. No set rules for the amounts, rates and types of replacement therapy can be made.

As already indicated, many factors influence the loss of fluids, electrolytes, erythrocytes, and so on, as well as the reaction of the patient. Therapy should be individualized. However, experience shows that a general pattern of loss and response may be anticipated, and on this basis a number of formulas have been devised as guides to replacement therapy. One of the most widely used is that of Evans,[9] based on the extent of the burn and the weight of the patient. The formula calls for 1 cc. of a colloid solution (such as dextran) per kilogram of body weight to be given intravenously during the first day, and one-half this amount the second day. Equal amounts of isotonic saline solution are given and, for an adult, 2000 cc. of 5 per cent glucose in water on each of the first two days. (Evans and colleagues have used sodium chloride solutions, whereas we, Moyer, Abbott, Reiss and others use a mixture of sodium chloride and sodium bicarbonate or lactate.) The saline and glucose solutions are given orally or intravenously, depending on the severity of the burn, state of the circulation, etc. If oral fluids can be taken, the saline is mixed equally with the glucose and water.

The upper limit of the volume of fluids which can be given safely is that quantity indicated by the formula for a 50 per cent burn. For a 70 kg. man, this would amount to 3500 cc. of colloid, 3500 cc. of saline, and 2000 cc. of glucose in water the first day, and 1,750 cc. colloid, 1,750 cc. saline, and 2000 cc. glucose in water the second day. The fluid replacement should roughly follow a schedule which approximates the rate of fluid loss: One-half the first day's requirement is to be given in the first four to six hours, one-fourth in the next six hours, and the final one-fourth in the next 12 hours. "*It is emphasized strongly that the simple formula presented here for calculation of fluid and salt requirements is only a guide to therapy and not to be considered an infallible rule*" (Evans). The rate and type of fluid administration are based on the clinical findings, the hourly output of urine, and the hemoglobin or hematocrit concentration (measured every four hours).

In patients with respiratory injury or serious cardiac disease, administration of colloid and salt should be limited to amounts which insure adequate response. The salt solution should be given orally if possible.

If severe shock already is present when therapy is begun, or if it develops during therapy, the fluid must be given rapidly to improve the circulation. Caution is necessary, of course, in infants, old persons, and patients with respiratory injuries or heart disease. The previously healthy adult in shock and with a large burn may be given as much as 2000 ml. in an hour without danger of overloading the circulation.

Evans has called attention to *acute gastric dilatation* as one important complication of shock. It may be manifested by failure of the patient to respond to apparently adequate fluid therapy. Decompression, lavage of the stomach, and replacement of the "lost" water and electrolytes will relieve the situation.

There is still controversy over the relative quantities of blood, plasma extenders, electrolytes, fluid, etc., to be used in treating burn

shock. Some workers would recommend less blood, others more saline, and some less dextran or plasma. As stressed earlier, controlled studies in patients are needed. Any "formula" must be used only as a guide to shock therapy; for any given patient, the therapy has to be individualized.

Additional Therapeutic Factors in Burn Shock

Vitamins—Limited experimental work with animals has indicated that the B complex vitamins and ascorbic acid may be helpful in burn shock. It also has been found that a great "depletion" of water-soluble vitamins occurs in man during burn shock as well as during traumatic shock. It appears reasonable to administer large doses of these vitamins during the early period.

Position—Raising the foot of the bed improves circulation to the brain, even though this maneuver may not alter the blood volume materially. It is especially important to do this during the first few minutes while more effective methods of treatment are being started.

Oxygen—There is no evidence that inhalation of 100 per cent oxygen alleviates the tissue anoxia of shock. Oxygen has been widely used in treatment of burn shock, but the only clear indication for its use is an injury of the respiratory tract or other forms of pulmonary dysfunction.

External temperature—Overheating and undercooling are detrimental to a person in shock. The best environmental temperature appears to be about 24° C.

Sedation—It has been noted that the death rate among burned dogs increased when the usual doses of morphine or barbiturates were given. These findings and others of a similar nature indicate that morphine and other sedatives should be used cautiously in patients with impending or actual burn shock. When used, administration by the intravenous route is essential, since absorption of subcutaneous or intramuscular medication is unpredictable. The action of anesthetics also is unpredictable; they are dangerous in burn shock. There is almost no occasion to use general anesthesia at the time of the first dressing.

Pressor drugs—These drugs are considered at present to be of no value in the treatment of burn shock, and they may be harmful.

Adrenocortical extract—There is no evidence to indicate beneficial effects from adrenocortical extract, ACTH or cortisone in most patients during the early phase following burns. A patient with adrenal exhaustion might be encountered rarely who would benefit from the use of adrenocortical extract. This general subject will be discussed later in the section on toxins in burn shock.

Factors in Burn Shock Other Than Fluid-Electrolyte Changes

Let us turn now to some other questions being studied by many investigative groups. One is whether or not factors other than changes in fluids, proteins and electrolytes are involved in burn shock. I am sure you are familiar with the fact that if shock is prolonged in some species of animal, particularly the dog and the rat, a hemorrhagic lesion develops in the intestine. Microscopically, and often grossly, there is evidence of mucosal necrosis. Certain antibiotics, given prophylactically, may prevent irreversibility of certain types of shock. The lowered bacterial and immunologic defenses of the animal in shock have suggested to some workers, principally Fine and his colleagues,[10] that when shock develops there is continued absorption of endotoxin from the intestinal bacteria into the blood stream. The endotoxin is highly toxic in the shocked animal because of the impaired function of the reticuloendothelial system and, the thesis states, although the animal went into shock initially because of fluid loss or blood loss, it dies of shock because of endotoxemia. It has been shown, for example, that animals which are given injections of THOROTRAST® and consequently have impaired reticuloendothelial function are more sensitive to hemorrhagic shock. Further, Fine has reported that blood or plasma of dogs and rabbits in irreversible shock (hemorrhagic or tourniquet) is toxic when transfused into recipient dogs and rabbits sensitized by having been reversibly shocked or pretreated with Thorotrast.

The thought that the toxic material arises chiefly from intestinal bacteria rests on the following evidence. (1) Certain antibiotics have greater prophylactic effectiveness when given orally than when given parenterally. (2) Hemorrhagic necrosis of the intestinal mucosa usually occurs in the irreversibly shocked dog and rat. (3) Irreversibility of hemorrhagic shock is delayed or prevented when the intestinal tract is separately perfused with oxygenated blood at normal pressure and rate during the period of systemic hypotension.[11] The possibility is not excluded that bacteria of other tissues also may be involved.

The idea that the toxic material is bacterial endotoxin stems from the following observations. (1) Certain physiologic and pathologic phenomena of shock are similar to those following endotoxin injection. (2) The shocked animal is very sensitive to injected endotoxin. (3) Animals made resistant to endotoxin by repeated injections of small doses are also resistant to hemorrhagic and drum shock. This endotoxin-induced resistance to shock is removed when Thorotrast is injected five hours prior to the hemorrhage—presumably because the Thorotrast impairs the function of the reticuloendothelial system. (4) Isotopically labeled endotoxin given orally is partially absorbed. (5) Blood and plasma from irreversibly shocked dogs, when transfused into properly sensitized recipients, lead to hemorrhagic necrosis of the intestine and a condition Fine has described as a generalized Shwartzman reaction, just as does injected endotoxin. (6) Finally, Fine and associates compared the effects of the lipopolysaccharide fraction isolated from the plasma of normal dogs with that of shocked dogs. This fraction was chosen because it is here that endotoxins, if present in the plasma, would be found. They noted that this fraction obtained from the plasma of irreversibly shocked dogs was toxic and that the toxicity of the plasma was confined to the lipopolysaccharide fraction. None of the concentrates of normal plasma were toxic by any of the tests employed.

It would seem that the germfree animal should be more resistant to shock than conventional bacteria-laden animals, but studies of hemorrhagic shock of rats and tourniquet shock of chicks have shown that this is not so. Experiments carried out with germfree animals by Zweifach and associates[12] at the University of Notre Dame and by McNulty and Linares[13] at the Walter Reed Army Institute of Research have shown that lethal shock can be induced in the absence of viable bacteria and that the course of events following the shock procedure, as judged by hemodynamic and pathologic changes, is similar whether viable bacteria are present in the animals or not. The presence of viable bacteria, therefore, is not essential for the development of fatal shock. However, these data do not exclude the possibility that viable bacteria, or their products, are important in the development of irreversible shock in the conventional animal, in which viable bacteria are obviously present. One cannot conclude that the mechanisms leading to death from shock are necessarily the same in the germfree and in the conventional animals, although the hemodynamics, pathology and mortality are similar in both situations. As Zweifach and Fine did, we considered the possibility that the small amount of endotoxin presumably present in the autoclaved diet of the germfree animals, and therefore present in their intestines, may be functionally equivalent in the germfree animal to the much larger amount of endotoxin present in the conventional animal. This would result from the presumed impairment of bacterial and endotoxin defense systems in the germfree animals. However, experiments with mice in the Department of Germfree Research at the Walter Reed Army Institute of Research have not supported this view; germfree mice have not proved more susceptible to bacterial endotoxin than their conventional counterparts.[14]

About 15 years ago, Prinzmetal and associates[15] in California conducted an experiment in which they found that when rats were burned deeply and severely, so that there was relatively little measured fluid loss, many died in shock in the first 24 hours and 48 hours. In contrast, when other rats were burned more lightly over a similar area, many more sur-

vived, although they seemingly lost much more fluid than the rats with deeper burns. The suggestion was made that this was consistent with the "production" and release of toxic material at the deeply burned site. Recent studies have been conducted using the air-pouch technics of Selye,[16] in which air is injected subcutaneously under the skin of the rat and the raised area is then burned. Fluid, presumably from the burned area, accumulates in the air pocket, is aspirated and tested biochemically and physiologically. Rosenthal[17] in Chicago interprets his findings as consistent with the liberation of toxic material from the burned skin. He has found peptides in the fluid as well as nucleotides and many other substances. It has been known for years that certain peptides get into the lymphatic circulation and presumably into the general circulation following burns.[18]

Malm[19] in our laboratory has shown that these findings may be significant in the problem of burn shock. He produced 50 per cent burns in a group of rats by holding their backs and abdomens against a hot plate at 240° C. This produces a deep third-degree burn. The injection of several proteolytic enzymes in doses which an unburned animal could handle without difficulty led to the death of a large number of the burned rats. Therefore, there is evidence not only that proteolytic enzymes are liberated from the burned area but also that the burned animal is highly sensitive to such enzymes.

Russian workers also have presented experimental evidence on this subject.[20] Dogs were flame-burned over 40 per cent of their body surface; the burns were third degree. An untreated group of these animals were all dead in 36 hours. Other animals were given ordinary dog serum, blood, dextran, or other colloids or exchange transfusions, but still 80 per cent died within one day, presumably of shock. Fluid replacement in these animals, therefore, did not prevent shock. However, the mortality rate was only 4 per cent among a group of these severely burned animals which were given serum taken from animals which had been burned less extensively and allowed to recover. The volumes of the "convalescent" serum and the serum from the ordinary animals were identical, and therefore the difference in the mortality rate cannot be ascribed to a difference in amount of fluid therapy. This suggests that the serum from a previously burned animal is highly effective when ordinary fluid replacement is ineffective. This experiment adds support to the idea that factors other than fluid loss are involved in shock. What these factors are, is another question. The Russian report advanced the idea that when tissue is burned the proteins are "denatured" or otherwise modified and are then toxic. Because of this they act as autoantigens and, if the burns are not too extensive, the animal will build "antibodies" to these antigens. Some of these "antibodies" will circulate in the serum, and when a freshly burned animal is given a transfusion of serum from an animal which has recovered from a burn, a passive transfer of antibodies is accomplished according to the Russian thesis.

This general problem blends into the question of the role of bacteria in burns. The Russian study also included the period when overt infection seems to play a dominant role, namely, the first, second and third weeks after burning. Animals were burned extensively by exposure to a flame for one and a half minutes. Those dogs which were given serum from unburned dogs were dead within 12 days. None of the burned dogs which were treated with "convalescent" serum were dead after 36 days.

The same type of result, but not as striking, was obtained by Malm[19] at our institution, but with rats instead of dogs. A very deep burn was produced by holding the anesthetized animal against a hot plate for a fixed time. Without special treatment except dextran and saline early, the mortality rate was 75 per cent after five days and 90 per cent by 9 or 10 days. Treatment with serum from animals burned eight weeks previously lowered the mortality to around 20 per cent. These observations, therefore, agree in principle with those in the Russian study, and suggest there is something special about the serum from animals which have recovered from their burns.

What is special about this serum from ani-

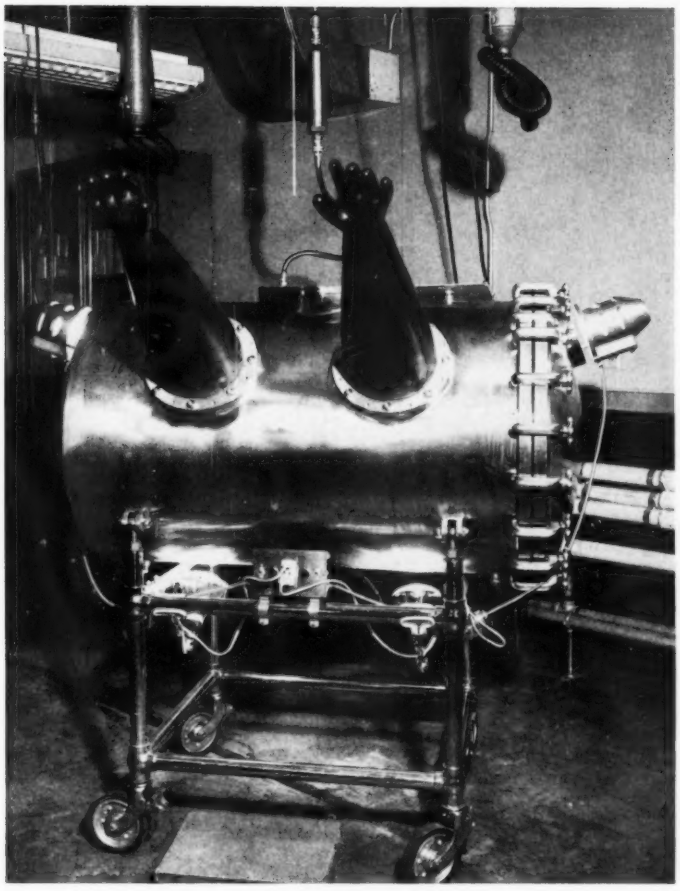


FIGURE 3. A Reyniers-type heavy stainless-steel germfree tank. The Department of Germfree Research at the Walter Reed Army Institute of Research uses 16 such one-man tanks as well as four similar tanks designed for two-man operation.

mals which have recovered from burns? The Russians advanced the idea that tissue proteins altered by the burn lead to "antibody" formation. Another possibility is that the serum contains "antibodies" to bacteria, because deep burns always become infected and thereby the animal may be building up "antibodies" to the infecting microbes. How can we distinguish experimentally between the effects of the burn itself and the effects of contaminating bacteria? We are fortunate to have a laboratory at the Walter Reed Army Institute of Research where we hopefully are able to do this.

The equipment at the Walter Reed Germfree Laboratory is modeled after that designed by Reyniers and Trexler at the University of Notre Dame. Large steel autoclaves are sterilized by steam under pressure in the ordinary way at the start of an experiment, before the animals are placed in them. The personnel are separated from the animals and tank environs by long rubber gauntlets attached to the autoclaves. Portholes permit one to see what is going on. The air is filtered mechanically to provide the animals with sterile air, or a heated sterilizing unit is used. The air then goes into the tank and exits through an exhaust trap filled with a germicidal solution. Animals have been kept germfree in our laboratory for as long as two years (figures 3 and 4). A small double-door autoclave attached to the main tank is used to get materials in and out of the isolators.

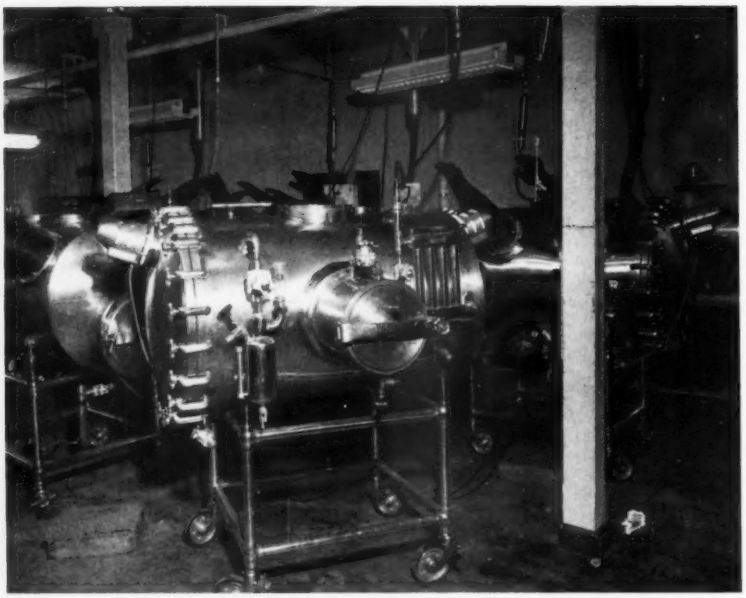


FIGURE 4. A rear view of a Reyniers-type germfree tank illustrating the tank autoclave through which materials are introduced into the chamber, the germicidal exhaust trap, and the four-barreled Fiberglas air filter.

A variety of animals are available for laboratory work, ranging from chickens and turkeys to guinea pigs, rats and mice to monkeys, sheep and goats. At Walter Reed we are working principally with rats, mice and guinea pigs.

We are now conducting studies with burned animals which are germfree. If bacteria are critically connected with the seemingly beneficial effect of "convalescent" serum when transfused into burned animals, serum from germfree animals which have recovered from burns should not have any beneficial effect when transfused into other burned animals, germfree or conventional. On the other hand, if "convalescent" serum from germfree animals does have a beneficial effect when given to germfree or ordinary animals, we will have to look for mechanisms other than bacterial ones to explain the effects of "convalescent" serum. I cannot tell you the results of these experiments, because they are just getting under way, but the potentials for experimentally segregating the effects of infection from the effects due to injury per se are at hand. I hope we will have the answer to this particular problem within a year or two.

Surface Treatment of Burns

Primary local treatment—The treatment of the burned skin has always been of paramount interest to the burned patient and his physician. The injury is obvious; the associated pain may be intense. The number of agents which have been applied to burns is vast. Although there is no universal agreement on the best primary local treatment, certain fundamental concepts are now widely accepted and have led to a more nearly unified view of treatment. It is clearly recognized that therapy of the local and general disturbances must be continually integrated from the time of injury to the end of convalescence.

Upon arrival at the hospital, the burned patient should be placed on a sterile sheet, his clothing removed by gowned and masked attendants, and his burns covered with sterile sheets. The area and depth of burn should be carefully estimated and recorded. He should be weighed, or a recent weight ascertained.

The possibility of respiratory damage or carbon monoxide poisoning should be evaluated. If the patient is conscious and in pain, but not intoxicated or in shock or suffering

from exposure to carbon monoxide or damage to the respiratory tract, morphine in small doses should be given slowly intravenously. At this stage absorption of medication given subcutaneously is unpredictable. If the aforementioned complications are present, DEMEROL®, not morphine, should be used. Appropriate "shock" therapy should be started.

When the patient's general condition is satisfactory, definitive local therapy should begin. One should try to correct the many physiologic and pathologic changes brought about by the burn. External and subcutaneous fluid loss should be limited, further contamination prevented, and infection controlled. Any surface application should be rapid and relatively easy to apply, and the least possible attention should be required thereafter. Spontaneous epithelization of second-degree burns should not be delayed; the separation of slough from deep burns should be hastened; the agent applied should not interfere with early surgical excision. There should be no adverse local or systemic effects. Absorption of many substances from the surface of both second-degree and third-degree burns has been demonstrated. Therefore, any agent applied to a burn either should not be absorbed or, if absorbed, must be nontoxic. At present, compression dressings or exposure to air seems to meet these requirements best.

Several years ago there was much debate about whether a dressing should be applied to a burn or whether it should be left open. This debate has simmered down with the realization that each method has certain virtues and disadvantages. The exposure method of treatment is not an easy method; it is not a treatment of neglect. Both methods have, of course, the same objective, to provide the conditions necessary for the quickest and safest healing. How this is theoretically accomplished by each method has been explained in other publications.[21-23]

We prefer the exposure method for burns of the face and perineum, and we prefer the compression-dressing method for burns of other areas, particularly extensive deep burns, circumferential burns of the trunk, and burns of the hands or feet. "The thoughtful surgeon can often employ either alone or both in conjunction to the patient's advantage. The effort, so far as I can determine now, should be focused on the production of a dry wound, free from infection, and early grafting of the full-thickness burn."[24] No fixed routine should be established for all cases. A clear understanding of the underlying principles will make it clear when variation in methods should apply.

Separation of dead tissue from deep burns—Deep burns should be covered with skin grafts at the earliest possible time. Until recently, most surgeons waited for spontaneous sloughing of the burned skin and formation of granulation tissue. This process is too slow and may lead to excessive scarring, contractures and deformities. In addition, until epithelization is complete, infection and disturbances in nutrition, formation of red blood cells, and other important bodily functions persist. There has been a growing recognition that one should do something rather than "let nature take its course."

Chemical debridement—Early excision and grafting of extensive burns, as stressed, constitute a major undertaking, requiring a skilled team, adequate operating-room facilities, and differentiation of deep burns and superficial burns, which is not always easy. So it has been the hope that some sort of chemical or enzymatic method of debriding these burned areas could be developed. Several preparations have been used successfully in animals for this purpose. However, as far as I know, there is not a single preparation which works effectively and predictably in man. We do not now have a method to accomplish so-called chemical debridement of a human third-degree burn. A few investigative groups are working on the problem of chemical debridement. The chief difficulty has been that the enzyme preparation either does not work at all on burned human skin or works "too well," producing destruction of blood vessels and hemorrhage.

Surgical excision—Immediate excision and skin grafting have been carried out occasionally. Theoretically, this is a sound procedure, because after a deep burn is excised and the wound successfully grafted, the area is covered

with skin in a week or 10 days. However, it has limited applicability because of the further physiologic upset it produces in a patient whose burn already may have caused shock. Further, it is often impossible to distinguish partial-thickness from full-thickness burns shortly after injury. Immediate excision, therefore, is indicated only in *obviously deep burns of relatively small area.* Relatively few deep burns are in this category.

When debridement is necessary, one should accomplish it surgically. I think the day is gone when one should allow a deeply burned area to slough gradually and wait for granulation tissue to appear before grafting. Now the problem should be attacked vigorously, with early excision and grafting.

A number of surgeons have excised and grafted burns as early as 2 to 10 days after injury when the patient's condition has stabilized. Allen[25] has detailed the technic. In brief, all damaged tissue must be removed down to normal fat, fascia and muscle. Grafting may be done immediately thereafter or delayed a few days. In patients with extensive burns, these operations should be done in stages. At the moment, this is the procedure of choice.[26,27] A skilled operative team is required. Spread of infection resulting from the operative excision is a possibility, and generally one should administer appropriate antibiotics prior to, during and after the operation.

Severely burned patients may pose difficult anesthetic problems. Cyclopropane is the anesthetic agent we have used most often. Patients with large denuded areas may lose heat excessively during an operation; in this situation appropriate countermeasures should be taken.

Homografts—Homografting has a definite application in the care of the severely burned patient, particularly in children. When excised or granulating areas are covered with skin, even temporarily, the patient's general condition improves so that by the time the grafts dissolve one can apply autografts successfully. Homografts cannot be made to "take" permanently by the use of ACTH or cortisone. Investigation in the field of homotransplantation is active, and if the conditions necessary for the "permanent take" of skin homografts can be established the care of the severely burned patient will be immensely improved!

Positioning—Proper positioning of the patient has been mentioned previously. Elevation of burned extremities, head, neck and upper thorax is useful in lessening edema and pain. The necessity for proper exposure of burns treated by the exposure technic has been emphasized. If the patient is to be kept in bed for more than a few weeks, steps should be instituted early to prevent foot drop. While supine, the patient's feet should rest at right angles against a footboard; while prone, his feet should hang over the edge of the mattress to maintain the right angle.

Physiotherapy—Intelligent physiotherapy can do much prophylactically and therapeutically in hastening rehabilitation of the burned patient. I will not attempt to detail the methods here; the measures to be used must be adapted to each patient.

Infection Associated With Burns

Infection is the major cause of death of patients with deep burns. While the slightly burned skin of superficial second-degree burns retains much of the resistance that normal skin has against bacteria, the slough characteristic of deep burns furnishes an excellent medium for bacterial growth. In addition, the patient's immunologic defense mechanisms may be significantly lowered. An abrupt drop in serum properdin and gamma-globulin levels and increased sensitivity to injected endotoxins and bacteria have been observed in burned animals. A severe disturbance in the phagocytal function of the reticuloendothelial system of the burned dog has also been described; previously phagocytized particulate matter is extruded and there is a progressive decrease in efficiency of phagocytosis.[28,29] It seems likely that the "resistance" of the severely burned patient also is lowered, but studies have been inadequate. The burned patient who is also exposed to significant irradiation is particularly sensitive to infection. I will not discuss in detail this very important problem here but refer the interested reader to the papers by Tumbusch and associates,[28] Colebrook, Dun-

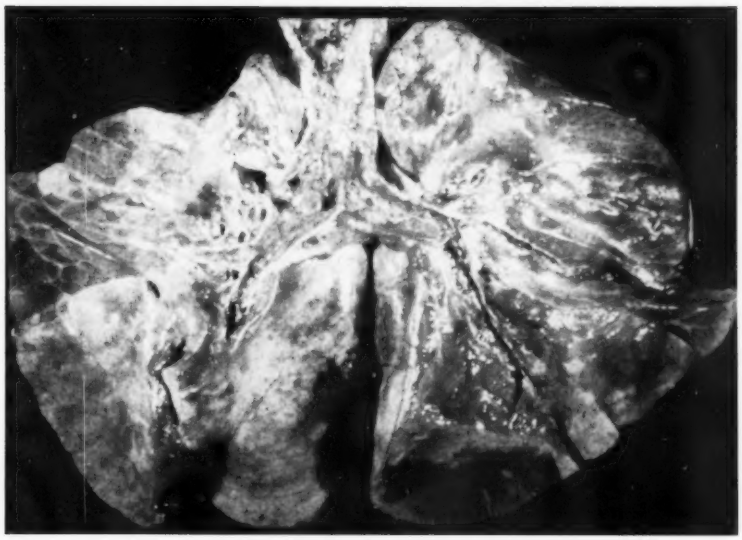


FIGURE 5. Lungs of a burned patient who died. Note plug of pseudomembranous material in the larynx. Microscopically there were plugs all the way down into the smaller bronchioles.

can and Ross,[29] Altemeier,[30] Kefalides and associates,[31] and Millican.[32]

Injury of the Respiratory Tract

I want to call attention to another important problem in burns quite apart from the burned skin. It concerns injury of the respiratory tract. Figure 5 illustrates the lungs of a burned patient who died. You can see a plug of material in the larynx, and microscopically there were plugs all the way down into the smaller bronchioles. This unfortunately can occur in a patient who is exposed to fumes in a fire for a fairly long period, and the important thing to remember is that although it is most often associated with facial burns it can occur in their absence.

After the Cocoanut Grove fire in Boston in 1942 we had three patients who had severe injury of the respiratory tract but no burns on the face.[33] Among the Cocoanut Grove victims the fundamental pathologic lesion was a necrotizing laryngotracheobronchitis with the formation of a pseudodiphtheritic membrane. Many of the respiratory passages were occluded by the pseudomembrane and viscid, sanguineous, mucoid exudate. There were scattered areas of congestion, atelectasis, emphysema and hemorrhage. The usual symptoms were sore throat, cough, hoarseness, dyspnea, cyanosis, wheezing, stridor, raising of sputum (mucoid, purulent, bloody) and restlessness. Scattered areas of dullness, hyperresonance and rales of all varieties were commonly found. Scattered areas of atelectasis, emphysema, congestion and consolidation were observed roentgenographically. Secondary pulmonary infections were few and usually mild, presumably because of the early and sustained chemotherapy with sulfonamides. The respiratory damage probably was due to irritants in the fumes and particles from the fire. From experimental studies by Moritz and associates,[34] it would appear unlikely that inhalation of hot air, as such, was an important factor. The victims who lost consciousness sustained the most severe respiratory damage; presumably they were exposed for the longest periods and thus inhaled the most fumes.

Injury of the respiratory tract associated with burns is not caused exclusively, however, by mass conflagrations. It may be a complication of burns received in an "ordinary" way. Cope and Phillips[35] recently reported that injury of the respiratory tract and its complications were the major causes of death among burned patients who received treatment at the

Massachusetts General Hospital during recent years.

Injury of the respiratory tract should be suspected in any patient who has inhaled large amounts of hot smoke, particularly if he has lost consciousness. This complication arises most often in association with facial burns but may occur in their absence. Many of the patients have singed nasal hair, soot on their faces, and burns of the nasopharynx. If respiratory injury is suspected, the patient must be watched closely. All personnel who come in contact with him should be masked. A tracheostomy kit should be kept at his bedside. The nose, nasopharynx, epiglottis, larynx and vocal cords should be examined. If the nasopharynx is burned, the nose should be swabbed with bland oil. It sometimes is helpful to have the patient gargle with a warm, soothing solution such as glucose in water.

Some of the symptoms to look for are dyspnea, cough and hoarseness, and these usually develop within the first several hours and become definite in six to eight hours. Respirations should be checked every half hour. The air in the room should be humidified. The patient should be turned frequently and encouraged to cough. If hoarseness, dyspnea or stridor develops, he should be placed in an oxygen tent. Helium-oxygen mixtures may be more easily breathed than 100 per cent oxygen. If there is evidence of bronchial spasm, intravenous aminophylline should be tried, or ADRENALIN® or ephedrine by nebulizer. Deep respirations should be induced for a few minutes every one to two hours by having the patient inhale a 10 per cent carbon dioxide-90 per cent oxygen mixture. Oxygen under pressure, together with a detergent and antispasmodic agent, may be useful. Generalized laryngotracheobronchial spasm may seize the patient suddenly and may kill him unless it is relieved immediately by tracheostomy or artificial respiration, or both. Tracheostomy is necessary if stridor, air hunger or other signs of laryngeal obstruction appear. If indicated, tracheostomy should be done early. If the question arises whether or not to perform tracheostomy, it should be done at once. But the problem does not end when this is accomplished, because there may be obstruction farther down in the bronchial tree and simple aspiration through the tracheal stoma may be ineffective. It may be necessary to put down a bronchoscope to remove a plug. The important thing is to be aware of the possibility of injury of the respiratory tract in association with burns. Suction through the tracheostomy tube should be applied repeatedly as needed; and when simple aspiration fails, bronchoscopic aspirations may succeed.

Restlessness of these patients may be due primarily to lack of oxygen, in which case the oxygen supply should be increased as already outlined. Or it may be due to pain (from surface burns), for which Demerol, not morphine, should be used. Or the restlessness may be due to fear and nervousness, in which case barbiturates should be given.

If the patient with injury of the respiratory tract also has extensive surface burns, appropriate fluid (colloid and electrolyte) should be given without hesitation, but cautiously, to prevent or treat shock. However, the patient must be watched closely for pulmonary edema.

Parenteral penicillin, in large doses, should be started when the patient enters the hospital. Antibiotic therapy might be altered later, if this is indicated by bacteriologic studies. Secondary pulmonary infection must be averted, or treated vigorously if it occurs.

Residual damage from the injury of the respiratory tract apparently is neither common nor severe.

Other Problems Associated With Burns

Many other important problems of the severely burned patient have not been mentioned. The metabolic and nutritional disturbances; alterations in the renal, adrenal, hepatic and cerebral function; changes in temperature-controlling mechanisms, and the anemia which so often complicates a severe burn are all basic problems. These have been discussed elsewhere.[36-38]

Possibilities for the Future

An experiment conducted about 15 years ago by Hoene[39] and his colleagues in Canada points up what we could conceivably hope for

in the future in regard to the prevention of burns. One limb of a rat was burned by placing it in hot water (48° C.) for two minutes and 15 seconds. Three days later, the preburned limb and another limb of the rat were placed in hot water (49° C.) for two minutes and 30 seconds. In the next several days there was no evidence of injury to the previously burned limb, whereas the other limb was obviously severely burned. This experiment suggests that something might be done to change the resistance of the skin or the tissues to burn injuries. The whole question of natural and acquired resistance to injury is now under active investigation. Conceivably, by appropriate pretreatment one might be able to produce a state wherein a burn injury that otherwise would be harmful or even lethal might be innocuous. Whether or not this will ever come to pass we certainly do not know, but I think this observation, which since has been repeated in several other laboratories, is too important and basic to be ignored.

Discussion

QUESTION: What is the current feeling regarding the use of cadaver skin for grafting?

DR. LEVENSON: In the early excision and grafting of a large burn, if there is not enough of the patient's skin available certainly the use of homografts is indicated, and these can be from living persons or suitable cadavers. These homografts (if viable) will "take" and will survive for periods up to eight weeks. During this time the wound is closed and clean. Hopefully, as the donor site heals one can replace the homograft with a fresh crop of the patient's skin and keep ahead of the sloughing of the homograft.

QUESTION: In the experiments in which the preburned leg of the rat was protected against subsequent burning, how long did the protection last?

DR. LEVENSON: This matter has not been studied adequately.

QUESTION: Do you ever use ACTH in the shock phase of a burn?

DR. LEVENSON: We have not used it. When a patient is severely burned, the adrenal gland is stimulated almost maximally. Conceivably there are situations where adrenal steroids, but not ACTH, might be used for the treatment of burn shock. If the patient had inadequate adrenal function prior to injury, certainly you would want to use cortisone or other suitable adrenal steroids. I have not seen documented early adrenal failure in a burned patient previously in good health. It is possible that hypofunction of the adrenal gland might occur, and the need for hormonal replacement therapy might become necessary.

Another situation where this form of therapy might be used would be a patient who is seen late, has severe burn shock, and fails to respond to appropriate therapy. You must use your clinical judgment, but if a patient is not responding to therapy that you consider really adequate in terms of fluid volume, electrolytes, colloids, acid-base correction, and so on, then cortisone in *pharmacologic* doses might be tried. A basis for this suggestion is the work I mentioned in regard to endotoxin. If endotoxin actually is getting into the circulation and if it really has a role in irreversible burn shock in man, its effects perhaps can be counteracted by large doses of cortisone. This same general problem may arise later in a burned patient's course if an overwhelming infection, particularly with Gram-negative organisms, is present.

QUESTION: In these animal experiments, has anyone ever cut off the burned extremity immediately to see if that would have any effect?

DR. LEVENSON: Yes, this has been done. Of course, if you cut off the extremity immediately, you can prevent burn shock. But this can be interpreted two ways: (1) By cutting off the burned extremity you have taken away the injured area; thus, there is no fluid loss; (2) you have cut off the source of "toxins."

The references cited in this paper are available in the author's reprints or on request to the Editorial Department, POSTGRADUATE MEDICINE, Essex Building, Minneapolis 3, Minnesota.

Management of Tetanus

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As recently as 1957,[1] the mortality rate in 462 cases of tetanus reported in the United States was 58 per cent. Despite recent rapid advances in medical knowledge and therapy, the mortality rate remains extremely high. The aims of management can be simply stated. They are early diagnosis,[2] early therapy and supporting care. The therapy of the patient with tetanus is essentially symptomatic.

Several considerations are important in determining prognosis and in planning the therapeutic regimen. Debility,[3] extremes in age,[4] incubation period,[5] and onset time[6] appear to be important factors. The prognosis in patients with pre-existing heart disease, respiratory disease, or poor nutritional status is worse than it is in patients without these disorders. The problems in management of both the aged and the very young contribute to a poorer prognosis. The mortality rate associated with an incubation period of more than 10 days is about 20 per cent, which, though significant, is considerably lower than the mortality in cases with an incubation period of less than 10 days. The onset time frequently has been considered to be a better prognostic criterion than the incubation period, since there may be no obvious injury or there may be multiple injuries that preclude a determination as to which of them harbored the source of infection. The onset time usually can be determined fairly accurately. It is the period from the appearance of the first symptom to the appearance of generalized spasms. When it is less than 24 hours the mortality is extremely high, in most instances over 80 per cent. When it is less than 48 hours the mortality rate is still about 50 per cent. The outlook for patients in whom the onset time is more than 48 hours is hopeful, and when the onset time is more than five days the mortality rate is about 10 per cent.

The rate of regression of symptoms in both mild and severe forms of tetanus is approximately the same. The period ranges from 11 to 47 days[7] with an average of about 24 days. It appears that a fixed time is necessary for removal of the tetanus toxin. Apparently "uncoupling" of the neurotoxin is related more to time than to quantity.

A program of therapy[8] should prevent the further absorption of toxin, eliminate any focus of infection, maintain an airway, main-

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tain adequate ventilation, prevent pulmonary complications, control spasms, maintain nutrition and fluid balance, and prepare for rehabilitation. Patients who survive should not have sequelae from tetanus.

Administration of Antitoxin

Antitoxin is given to neutralize circulating toxin and prevent further absorption of the toxin into the central nervous system. No uniform method of administration has been devised. It is doubtful whether local administration at the site of injury has any advantage over intramuscular or intravenous administration. Intrathecal injections should not be used.

Before administration of antitoxin, an intradermal sensitivity test or a conjunctival sensitivity test or both should be performed. The limitations of these tests and a detailed account of other aspects of antitoxin administration are given in an excellent report to the Council on Drugs of the American Medical Association.[9] Epinephrine, aminophylline and oxygen should be immediately available before antitoxin is given.

Patients who exhibit sensitivity can be desensitized. The Mayo Clinic[10] recommends the prior administration of an antihistamine and the use of an ACTH drip (30 to 60 units) with 0.5 mg. of 1:1000 epinephrine in an intravenous solution of 1000 ml. of 5 per cent dextrose. This infusion is given rather briskly and after 30 minutes 0.1 ml. of diluted antitoxin (1:100) is given subcutaneously. If no reaction occurs after 10 minutes, a larger dose of the diluted antitoxin is given, 0.2 ml., then 0.4 ml., and finally 0.8 ml. If this dilution of antitoxin does not produce a reaction, a dilution of 1:10 of the tetanus antitoxin is given in a similar series of doses at 15 minute intervals. If no reaction occurs, a 0.1 ml. dose of undiluted tetanus antitoxin then is given intramuscularly. If there is no reaction, the dose of undiluted serum is increased to 0.3 ml., 0.5 ml. and finally 1.0 ml. at 15 minute intervals. One milliliter is administered every 15 minutes until the total dose has been given. If reactions occur, the dose is decreased by one or two increments and then increased more slowly. Bovine serum, when available, should be used in persons sensitive to horse serum.

Adequate blood levels[11] are obtained with injections of 80,000 to 100,000 units of antitoxin. Larger or repeated doses increase the incidence of serum reactions. There appears to be an inhibitory effect on the production of active immunity if antitoxin and toxoid are given simultaneously. The use of toxoid in a case of tetanus can be delayed until the patient is convalescent. Active immunity must be given, since recurrent tetanus[12] is a relatively frequent occurrence.

Care of the Wound

Good surgical principles[13] should be observed in the care of the wound. Necrotic tissue or tissue with inadequate blood supply should be removed. Good hemostasis should be obtained to prevent formation of hematoma. Since the tetanus bacillus, *Clostridium tetani*, is an anaerobe, the medium for growth usually is supplied by devitalized tissue or an area of infection resulting from symbiotic bacteria. Penicillin is bactericidal to the clostridial organisms, and a wide-spectrum antibiotic can be used to cover the symbiosis.

There is no evidence that amputation at a distance from the site of injury[14] will improve the prognosis. All grossly infected wounds should be debrided widely. Particularly hazardous are burns, compound fractures, puncture wounds and any wound that has had contact with the soil. Culture of the wounds should be done whenever possible.

Tracheostomy

Tracheostomy has been advocated in the management of all patients with tetanus.[15] Some clinicians have modified this view since the advent of chlorpromazine[16] and meprobamate, but for the physician who encounters a patient with tetanus only occasionally it might be wise to recommend prophylactic tracheostomy in every case. Absolute indications for tracheostomy[17] are as follows: (1) all cases in which the incubation period is less than 10 days or the onset time is less than 48 hours; it can be anticipated that under these conditions the disease probably will be

severe; (2) patients with respiratory spasms longer than 15 seconds in duration; (3) patients who are unable to swallow pharyngeal secretions; (4) patients who are unable to cough and clear tracheobronchial secretions; (5) the presence of excessive tongue biting or edema of the tongue leading to mechanical obstruction of the upper airway; (6) the presence of coma, usually due to oversedation; (7) the presence of any pulmonary complication; (8) patients in whom peripherally acting muscle relaxants are being used; (9) inspiratory stridor; (10) laryngeal obstruction due to spasm or the presence of secretions.

Tracheostomy may be done under local anesthesia, but where adequate facilities are available the procedure is better accomplished with the use of peripherally acting muscle relaxants, thiobarbiturates and endotracheal intubation. Wound debridement can be accomplished at the same time.

The presence of a tracheostomy does complicate the clinical management.[18,19] Inadequate humidification of the inspired air creates a major problem. Tracheobronchial secretions become dry and tend to crust the air passages and the tracheostomy tube. Frequent deep tracheal suctioning in an attempt to remove the secretions is traumatic and may lead to bleeding within the trachea or major bronchi and eventually to tracheitis sicca. This sequence of events can be avoided by providing adequate humidity. Heated mainstream[20] nebulization, especially during assisted ventilation, is the ideal mechanical method of producing adequate humidification. If a heated mainstream nebulizer is not available, tracheostomy masks, steam tents, expired air heat exchangers[21] or other technics are essential to aid humidification.

Saline irrigation of the trachea can be used to loosen and remove encrusted secretions. Initially, 5 to 10 ml. of warmed saline is instilled. Larger volumes of 20 to 30 ml. are used if the smaller volumes are tolerated. Much of this saline will be absorbed rapidly, and the remainder is removed with careful deep tracheal suctioning. It is advisable to use catheters which can be inserted selectively into both the right and left main stem bronchi. Good postural drainage by placing patients in the full lateral position is essential. Chest pounding is helpful in mobilizing tracheobronchial secretions. Bronchoscopy can be done relatively easily and atraumatically through the tracheal stoma.

Sedation

The backbone of symptomatic therapy is aimed at maintenance of a patent airway and a normal respiratory exchange. Muscular spasm interfering with a patent airway and ventilation must be controlled, without concomitantly depressing respiration. Barbiturates, paraldehyde, chloral hydrate, opiates, tribromoethanol and other sedatives are of limited value. In only the mildest cases do these drugs control spasms without producing excessive respiratory depression. There must be sufficient control of reflex spasms to permit the accomplishment of routine nursing procedures. These include turning for postural drainage, deep tracheal suctioning, bladder and bowel care, blood pressure measurements, and feeding via a nasogastric tube, all of which can be stimulating procedures to the patient with tetanus.

With the exception of the peripherally acting muscle relaxants, the phenothiazine derivatives[22] have provided the most effective control of reflex spasms. Meprobamate[23] appears to be the drug of choice since it effectively abolishes reflex spasms due to noise or light. It does not appear to abolish seizures resulting from bladder or bowel distention, mucus in the tracheobronchial tree, or proprioceptive stimulation from turning the patient. Meprobamate is given intramuscularly in an 8 per cent solution in polyethylene glycol. Single injections of 400 mg. are given to adults every three or four hours. The dose is titrated to provide the necessary control. Proportionately smaller doses are used in children and infants. Since there is a wide range of safety, the dosage can be adjusted by trial and error. When this does not provide adequate control, chlorpromazine (25 to 50 mg.), promethazine (25 mg.) and pentobarbital (30 to 60 mg.) can be added as needed. These may be given intramuscularly or intravenously.

Drugs such as mephenesin[24] and methocarbamol[8] which diminish skeletal muscular tone by acting on the central nervous system have been used to control muscular spasms. However, adequate control can be obtained only through intravenous administration, thereby limiting their application in therapy.

Peripherally acting muscle relaxants such as curare, gallamine and succinylcholine cannot be used effectively without producing respiratory depression. Their use is reserved for patients[25] in whom generalized spasms cannot be controlled without producing inadequate ventilation. These patients must be managed by a team experienced in handling respiratory emergencies, skilled in the use of respirators, and practiced in administering relaxants.

Other Important Aspects of Management

Constant supervision by nurses is essential during the acute stage of tetanus. Initially an intravenous infusion should be maintained until the effects of therapy are evaluated; this also provides a route for emergency administration of drugs. Daily intramuscular injections of 600,000 units of penicillin are adequate. Other antibiotics can be added as specific indications arise.

A cleansing enema should be given as early in the course of the disease as practicable. Urinary retention catheters should not be used unless absolutely necessary. Most of the patients will need nasogastric tubes for supplemental feeding, since swallowing usually is impaired. Attempts to administer fluids or solids orally should be deferred until there is virtually no difficulty with swallowing. A carefully selected diet should be used to prevent either diarrhea or fecal impaction. Supplemental vitamins should be given.

The hemoglobin level should be checked three times a week, since anemia frequently develops. A routine electrocardiogram is taken following admission. Cardiovascular complications occur frequently in the older age group. A posterolateral and a lateral chest roentgenogram are taken in convalescence, since compression fractures[26] of the thoracic vertebral bodies are common and may give rise to symptoms. Active and passive physiotherapy is used as early as possible to reduce limitation of joint motion and to speed rehabilitation. Medications are reduced gradually as convalescence progresses. When problems of upper airway obstruction and removal of tracheobronchial secretions no longer exist, the tracheostomy tube is removed.

Summary

Recovery of the patient with tetanus should be anticipated. An over-all plan of management should be formulated for each case. Consultation services should be used freely. Successful therapy depends on competent nursing care and intelligent supervision by the physician. Prevention, recognition and treatment of respiratory complications are needed if mortality is to be reduced significantly.

Discussion

QUESTION: What would you say is the usual lethal mechanism in tetanus?

DR. OSWALD: My impression is that the patient almost invariably dies a respiratory death. Occasionally cardiac failure occurs, but this is probably secondary to hypoxia, hyperpyrexia with tachycardia, or pre-existing heart disease.

QUESTION: One area of the problem that I think should be mentioned, for the sake of completeness, is the propaganda for widespread use of toxoid. Throughout the state of Iowa, where I come from, you would be surprised how many farmers, for example, have never heard of tetanus toxoid.

DR. OSWALD: Unfortunately I failed to mention this. It is the only way we are ever going to eradicate tetanus. In every patient who comes into your office you should consider initiating active tetanus immunization.

QUESTION: How about boosters?

DR. OSWALD: You can expect to get effective antitoxin levels in patients who have had a toxoid booster within the past five years, and occasionally with an even longer interval between boosters. There are persons who will not get active immunity from toxoid, but fortunately they are few in number. Reactions to toxoid also occur infrequently.

QUESTION: Who should get tetanus antitoxin prophylactically?

DR. OSWALD: If a wound is clean and can be considered sterile, do not give antitoxin; begin active toxoid immunization.

QUESTION: There is a legal implication here.

DR. OSWALD: The Mayo Clinic, as well as others, advocate this as an accepted method. Since we know reactions to antitoxin can be fatal, we can legitimately weigh the risk of one against that of the other. When you have decided not to give antitoxin, and know why, I do not think you can be implicated. In any wound which is doubtful, antitoxin is given. Routinely, 3000 units are used; whether or not this is an adequate dose or the best dose is still not determined. At least 30,000 units are given whenever it is impossible to debride a wound adequately, especially if there is a possibility that this might be a focus of tetanus infection. In essence you then are trying to provide neutralization of circulating toxin.

QUESTION: Well, in Iowa I think nearly everybody has an occupational hazard.

DR. OSWALD: Then by all means you should give tetanus toxoid routinely to all patients. If you are responsible for providing continued active immunization, you should see that toxoid is given every five years.

I would like to read you portions of the recommendations of the Mayo Clinic. Active immunization is now advocated for all those exposed to occupational risks of infection, all infants, convalescents of clinical tetanus, all persons with a past history of allergy, and injured persons previously actively immunized, to whom a booster dose of tetanus toxoid should be given and not prophylactic antitetanic serum.

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SCIENTIFIC EXHIBIT

DEEP VENOUS THROMBOSIS

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STANLEY M. ROGOFF,
CLAY E. PHILLIPS, JR.
AND WALTER J. PORIES

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University of Rochester Medical Center,
Rochester, New York

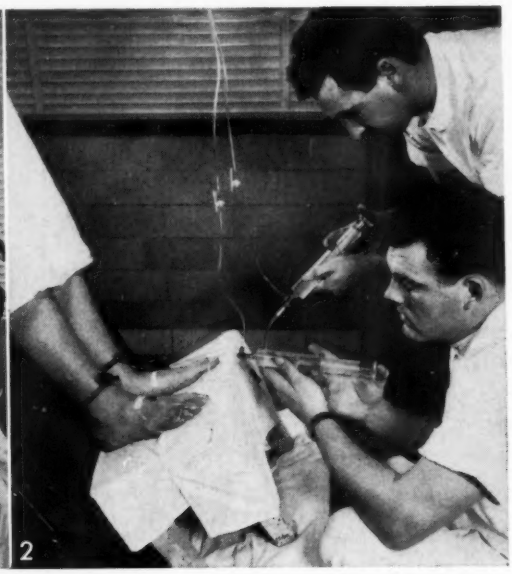
Adapted from an exhibit designed and rendered by R. D. Howe, Department of Medical Illustration; photography by J. Gaughan and M. Orser, Department of Photography, University of Rochester Medical Center, Rochester, New York.

Study supported by the Health Association of Rochester and Monroe County.

Are You Always Sure of Your Diagnosis of Venous Thrombosis?

THE superficial veins of the leg are readily accessible for examination, but the deep veins are hidden within the muscle compartments. Phlebography provides a means of visualizing deep veins, and can assist in making a correct diagnosis.

Method of Phlebography



1.

Patient is placed in a semierect position (60 degrees for suspected thrombosis in vein of calf, 30 degrees for suspected thrombosis in femoral or iliofemoral vein).

A needle or polyethylene tubing is introduced into any superficial vein on dorsum of the foot, and connected to a saline drip.

A rubber tourniquet is applied tightly around the ankle.

2.

Forty cubic centimeters of 50 per cent HYPAQUE® sodium is injected over a one minute period.

A long (14 by 34 in.) film is exposed.

3.

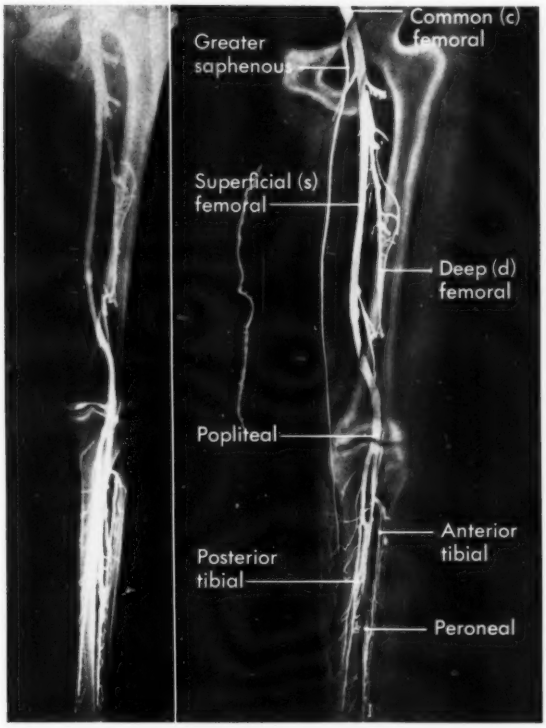
If ambulatory prior to examination, patient raises himself on toes from 3 to 10 times.

A second long film is exposed.

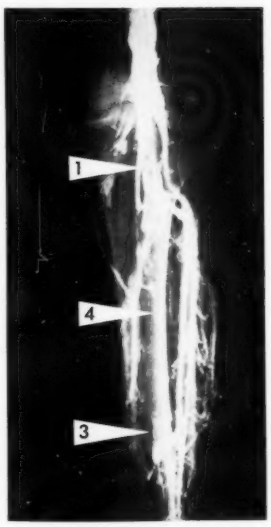
Patient is returned to horizontal position, and saline solution is flushed through the needle.

Diagnosis of Deep Venous Thrombosis

Normal Phlebogram



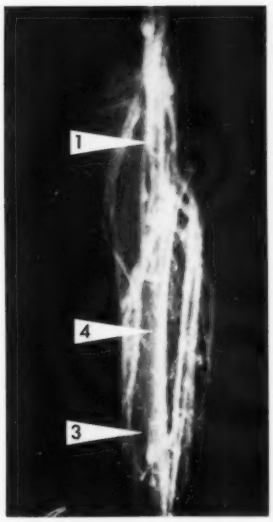
Typical Thrombi



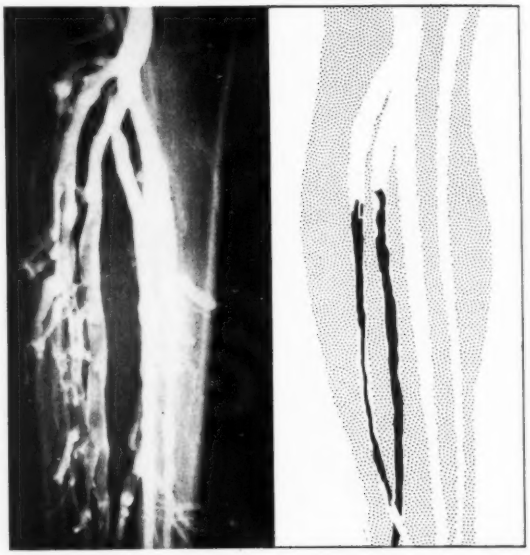
Before Exercise **After Exercise**

Characteristics

1. Thrombus defect has sharp margins in a heavily opacified vein.
2. It is seen on at least two roentgenograms.
3. Smaller bubblelike thrombi may be seen distally.
4. A long segment of the vein may not be visualized.



Diagnosis of Deep Venous Thrombosis (Continued)
Clinical Signs Are Frequently Unreliable

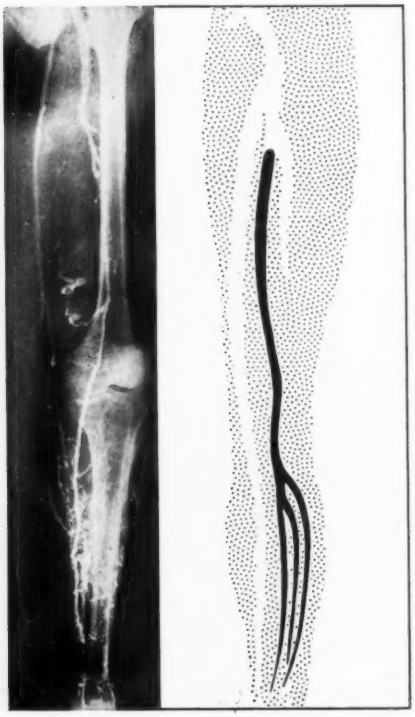


Thrombosis in Vein of Calf

Swelling in calf absent in 35 per cent, minimal in 55 per cent

Tenderness absent in 20 per cent

Homans' sign absent in 50 per cent

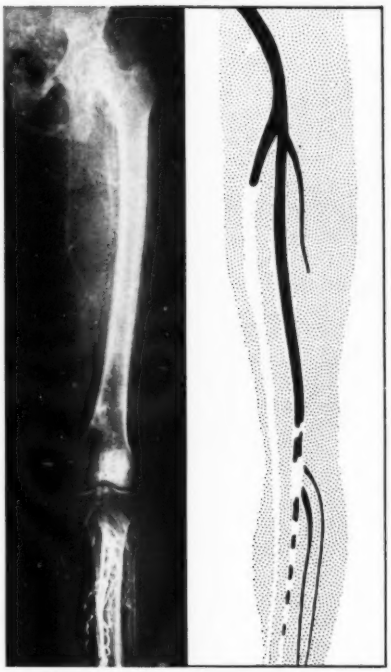


Thrombosis in Femoral Vein

Swelling in calf minimal in 10 per cent, in thigh minimal in 30 per cent

Tenderness absent in 20 per cent

Homans' sign absent in 30 per cent



Thrombosis in Iliofemoral Vein

Swelling in calf moderate in 20 per cent, in thigh moderate in 15 per cent

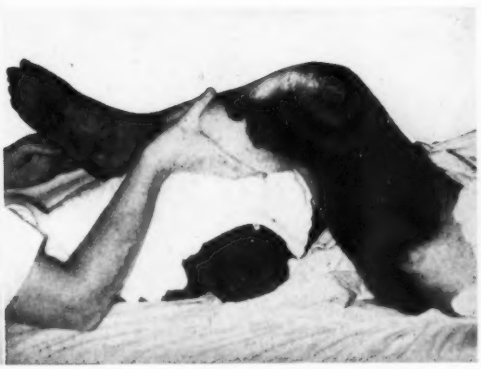
Tenderness never absent

Homans' sign absent in 50 per cent

No Vasospasm

With Vasospasm

With Gangrene



Problem Cases

1.

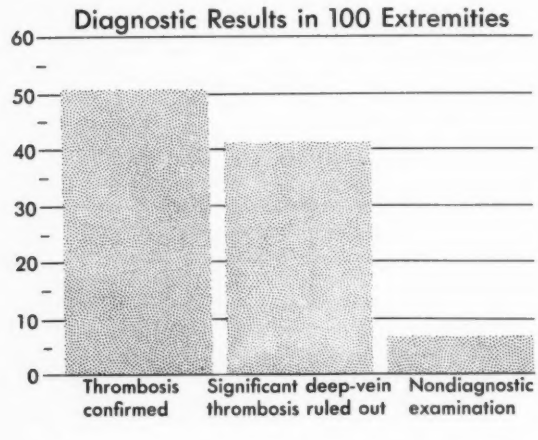
2.

3.

Problem 1. Repeated pulmonary emboli in 52 year old woman
Physical signs: No swelling or tenderness, Homans' sign absent
Phlebogram: Thrombi demonstrated in peroneal vein
Treatment: Ligation of femoral vein

Problem 2. Pain in calf after gastrectomy in psychoneurotic 44 year old woman
Physical signs: No swelling, minimal tenderness, equivocal Homans' sign
Phlebogram: Thrombi in veins of calf extending into popliteal vein
Treatment: Anticoagulants and bed rest

Problem 3. Pain in thigh after osteotomy in 42 year old woman
Physical signs: Swelling in thigh and calf, tenderness in medial and lateral thigh, Homans' sign absent
Phlebogram: Normal
Treatment: Observation. Deep wound abscess became obvious



Reason for Phlebograms

This procedure is used to determine source of pulmonary emboli and to assist in correct diagnosis in patients with suspected venous thrombosis.

CLINICAL STUDY

Evaluation of Librium® as a Preanesthetic Medication

CARL A. COPPOLINO* AND GEORGE WALLACE†

Methodist Hospital, Brooklyn

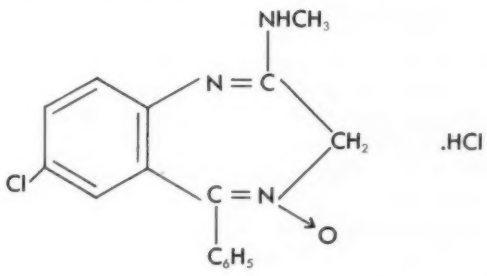
Librium, a new psychotherapeutic agent unrelated chemically or pharmacologically to other known tranquilizers or antidepressants, was administered in a dose of 25 or 50 mg. in combination with a sympathomimetic drying agent as preanesthetic medication to 400 patients undergoing elective surgical procedures. It alleviated apprehension effectively. Optimal results were achieved with the 50 mg. dose. There was no evidence of alteration in blood pressure, of respiratory depression, or of influence on anesthetic requirements.

THE use of tranquilizers as preanesthetic drugs has reduced the respiratory depression, nausea, vomiting, dizziness, dysphoria and addiction associated with administration of narcotics and barbiturates. Nevertheless, certain side effects, particularly hypotension, resulting from even single doses of the more potent phenothiazines[1,2] as well as from other members of this class of compounds[3] have limited their usefulness in surgical procedures.

The present investigation was undertaken to evaluate a new psychotherapeutic drug, methaminodiazepoxide (LIBRIUM®),‡ as a preanesthetic medication. This drug was selected because of generally impressive reports of its safety and effectiveness in relieving anxiety and tension.

Chemistry of Librium

Librium (methaminodiazepoxide) is 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide hydrochloride. It is a colorless crystalline material which is highly soluble in water but unstable in solution. The powder must be protected from light. As can be seen from the structural formula, Librium is chemically unrelated to any known tranquilizers.



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CARL A. COPPOLINO

GEORGE WALLACE

Pharmacology of Librium[4]

Librium exhibits tranquilizing, muscle-relaxing and anticonvulsant properties in laboratory animals and produces a unique calming effect on vicious or agitated monkeys. It lacks the autonomic blocking effects of chlorpromazine and reserpine, is more potent than meprobamate as a muscle relaxant, and does not induce the hypnosis of the barbiturates, although its anticonvulsant properties are similar to those of phenobarbital.

In anesthetized dogs, Librium had no effect on blood pressure when administered intravenously in a dose of 4 mg. per kilogram of body weight, and only slight depressor effects were observed with doses of 8 to 16 mg. per kilogram. Heart rate was not affected by doses up to 4 mg. per kilogram, and only slight slowing occurred with higher doses.

Clinically, methaminodiazepoxide reduces anxiety and tension without impairing higher mental functions or significantly altering blood pressure.[5] Onset of action is rapid, the first observable therapeutic effects having been reported to occur within a few minutes.[6,7] The need for narcotics was definitely decreased when the drug was used in narcotic addicts.[8]

Method of Study

In the present pilot study, 400 unselected patients undergoing all types of surgical procedures were given Librium as preanesthetic medication. Their ages ranged from 14 to 91 years. Physical status was extremely variable, the only constant factor being that the surgical procedures were elective.

In order to determine the most effective dose of Librium, the 400 patients were divided into two equal groups. Group A received 25 mg. and group B 50 mg. of the drug. Librium was administered orally one and a half hours prior to the onset of anesthesia. Each patient received either 25 or 50 mg. in combination with an intramuscularly administered sympathomimetic drying agent.

Anesthesia was induced by both inhalation and regional technics. The inhalation agents used included thiobarbiturates, cyclopropane, ether and halothane. The regional technics employed were subarachnoid block, brachial plexus block and digital block.

The psychic state, degree of somnolence, respiration, blood pressure and pulse rate were observed before and after administration of Librium. The presence or absence of nausea and vomiting, effect on pain, and effect on subsequent use of anesthetic drugs were also recorded.

Sixty-four (32 per cent) of the 200 patients receiving 25 mg. and 75 (37.5 per cent) of the 200 patients receiving 50 mg. were judged as being apprehensive the night prior to operation.

Results

Psychic state—Evaluation immediately prior to anesthesia revealed no apprehension in any of the 400 patients (table 1).

Somnolence—One hundred and forty (70 per cent) of the 200 patients receiving 25 mg. and all of the 200 receiving 50 mg. of Librium were found to be somewhat somnolent prior to the onset of anesthesia. In spite of somnolence, there was no evidence of a lack of response to environmental stimuli.

Respiration—Comparison of premedication and postmedication records of respiratory status did not reveal evidence of respiratory depression.

Blood pressure and pulse rate—There was no evidence of alteration in either blood pressure or pulse rate in the immediate preanesthetic period.

Nausea and vomiting—Nausea and vomiting did not occur.

Effect on pain—While the effect on pain was more difficult to evaluate, it was felt that

TABLE 1

EFFECT OF LIBRIUM AS PREANESTHETIC MEDICATION IN 400 ELECTIVE SURGICAL PROCEDURES*

	25 MG.	50 MG.
Lack of apprehension	100 per cent	100 per cent
Presence of somnolence	70 per cent	100 per cent
Respiratory depression	None	None
Change in blood pressure or pulse rate	None	None
Nausea and vomiting	None	None
Effect on pain	Little or none	Little or none
Potentiation of anesthetic agents	None	None

*A dose of 25 mg. of Librium was given orally to 200 patients, and a dose of 50 mg. was given to 200, in combination with a sympathomimetic drying agent administered intramuscularly one and one-half hours prior to anesthesia.

the patients exhibiting pain prior to anesthesia and operation obtained little or no relief of pain.

Effect on subsequent use of anesthetics—The requirements for anesthetic drugs did not appear to be decreased appreciably. In addition, there did not appear to be a potentiation of the muscle relaxants used (curarelike drugs and succinylcholine).

Summary

Our initial investigation indicates that in the preanesthetic patient Librium produces a very desirable state of acceptance of the anesthetic and operative intervention. The ability of Librium to alleviate apprehension seems to be its outstanding characteristic. While either 25 mg. or 50 mg. administered in combination with a sympathomimetic drying agent one and a half hours prior to anesthesia was effective in this respect, optimal results can be achieved with 50 mg. At this dosage level all patients were somewhat somnolent yet there was no lack of response to environmental stimuli. Since one of the cardinal considerations in preanesthetic medication is the creation of a nonapprehensive state without over-all depression, it would appear that Librium is notable in satisfying this particular requirement.

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CLINICOPATHOLOGIC CONFERENCE

Report From Veterans Administration Hospital, Hines, Illinois

Edited by William J. Donnelly, M.D., Chief, Section of Hematology

Case Report

ON April 3, 1959, a 33 year old truck driver was transferred from another hospital to Hines Veterans Administration Hospital for orthopedic, plastic and neurosurgical treatment of conditions resulting from chronic paraplegia. He had severe contractures of the lower extremities, large decubitus ulcers of the sacrum and trochanters, and pronounced spasm of the adductors of the lower extremities.

As a result of a fall in August 1954, the patient had sustained compression fractures of T10 and T11 and a physiologically complete transverse myelopathy. He was admitted to Hines in that month with an infection of the urinary tract and a calculous formation in the bladder. The same symptoms were present in January 1957, when he was again admitted to Hines. In addition, he had increasing spasms of the adductors of the lower extremities and spastic dislocation of the left hip. A bilateral obturator neurectomy was performed. In August of that year, the patient was hospitalized a third time at Hines with spasms of the adductors and flexors of the lower extremities. Infection of the urinary tract and a calculous formation in the bladder also were present. In February 1959, the patient was admitted to another Veterans Administration hospital with a large decubitus ulcer formation and an acute infection of the urinary tract. Calculi were removed from the bladder and blood transfusions were administered to the patient.

The patient's history before 1954 included no clinically significant illnesses, injuries, exposures or habits, except for vague abdominal pains diagnosed and treated as peptic ulcer by a private physician.

At the time of his last admission to Hines, the patient was pale and thin and appeared chronically ill. He had severe heel-to-buttock contractures of the lower extremities and large trochanteric and sacral decubitus ulcers. Otherwise, general physical examination gave negative results.

Laboratory data—Blood chemistry studies performed on May 18 showed that nonprotein nitrogen was 29.7 mg.; total protein was 8.6 gm., with 5.1 gm. albumin and 3.5 gm. globulin. On June 30, further studies showed the

TABLE 1

LABORATORY DATA

TESTS	DATES									
	4/27	5/18	5/25	6/8	6/15	6/20	6/22	6/30	7/1	7/2
Urinalysis										
Color	Straw		Straw	Straw		Amber	Yellow			Straw
Specific gravity	1.002		1.003				1.010			
Protein	0		0	0		1+	0	2+	2+	2+
Sugar	0		0	0		0	0	0	0	0
White blood cells per high-power field	0		Occasional	0		Many	0	Many	Many	Many
Red blood cells per high-power field	0		0	0		Occasional	0	Many	Many	Many
Bile								0	0	0
Urobilinogen								Trace	0	0
Hematology										
Hemoglobin (gm.)		11.7			12.0	11.3	11.3	11.3		11.0
Hematocrit (per cent)		41			39	39	41	41		32
White blood cells (x 10^3)		8.0			7.1	7.9		11.0		14.8
Neutrophils								84		84
Lymphocytes								15		16

total protein to be 6.1 gm., with 2.7 gm. albumin and 3.4 gm. globulin. On that same day, direct bilirubin was 3.5 mg. and indirect bilirubin was 2.9 mg. Alkaline phosphatase was 11.4 Bodansky units; the thymol turbidity was 13; amylase was 39 units. Sodium was 128 mEq., and potassium was 3.9 mEq. On July 1, the nonprotein nitrogen was 29; the cephalin-cholesterol flocculation in 48 hours was 4 plus, and carbon dioxide was 12.6 mEq. Other laboratory data are summarized in table 1.

Posteroanterior x-rays of the chest made on April 6 and June 23 showed no abnormalities. On June 30, a posteroanterior view revealed patchy densities throughout most of the left lung field; these had resolved by the time follow-up x-rays were made on July 1 and 3. X-rays of the knees and pelvis showed diffuse osteoporosis. On June 24, an x-ray of the upper gastrointestinal tract revealed hypertrophic antral folds.

Hospital course—In addition to receiving vigorous general medical and nursing treatment for the urinary tract infection and the decubitus ulcers, the patient initially was given tetracycline, chloramphenicol, FURADANTIN®, ferrous sulfate and 1500 cc. of blood.

During April, the patient had a fever ranging from 100 to 101.5° F., and nausea and emesis occurred. These symptoms abated for three weeks in May. During June, he was again febrile (100 to 103° F.) and had associated but intermittent nausea and emesis. Hiccups, restlessness, emotional lability and involuntary contractions of the upper extremities appeared during the last several days in June. From June 25 to 29, he was given 400

mg. meprobamate four times daily. In addition, 50 mg. chlorpromazine was given every six hours on June 27 and 28. The patient became jaundiced on June 29. Examination on the next day disclosed that blood pressure was 90/60 and the pulse was 122. A profuse diaphoresis was noted. The heart and lungs were normal. A questionable mass was felt in the periumbilical area; the liver, spleen, kidneys and gallbladder could not be palpated. The patient was dehydrated and delirious. Although the sensorium cleared completely on the afternoon of June 30, by the next morning the patient was quite somnolent again. On the following day, he was deeply jaundiced and comatose, and he had a convulsion. On July 5, the blood pressure could not be obtained and convulsions occurred frequently. The patient died following a brief period of Cheyne-Stokes respiration.

Discussion

DR. MITCHELL A. SPELLBERG (associate professor of medicine, University of Illinois College of Medicine): This young man had been a paraplegic for many years, and he had the degenerative processes, multiple infections, urinary calculi and osteoporosis associated with this type of grave disability.

In considering this case, let us first discuss the problem of nausea and emesis, which occurred frequently in April. Why did he have nausea and emesis? Was this condition due to reactivation of an ulcer, to pyloric obstruction, or to infection and toxemia? In my experience, I have not observed nausea and emesis as a result of a duodenal ulcer unless it is complicated. Of course, if it is complicated by pyloric obstruction, emesis ensues, and the patient usually vomits voluminous amounts of gastric contents. The vomiting is very typical; it occurs many hours after meals or in the middle of the night. Since this patient's emesis is not described in detail, I assume that he did not vomit large amounts and that he vomited shortly after meals. Sometimes, the patient with a gastric ulcer may vomit shortly after eating, especially after ingesting irritating food. The patient with a duodenal ulcer almost invariably feels better immediately after eating; the vomiting occurs much later. If the vomiting is due to a toxic factor, the patient is very sick.

Now, this man was febrile, and he was receiving antibiotics, which may cause nausea and emesis. I assume that the emesis was not due to the gastrointestinal disease per se, but to the infection plus the antibiotics. Any of the antibiotics, particularly Furadantin, may cause nausea and vomiting.

There was no bloody or coffee-ground vomit. Why then was this patient given 1500 cc. of blood? His hemoglobin level was fairly good, but he also had been given transfusions at another hospital. Why? Did he have a grave anemia? Did he have a severe blood loss? Was the blood given just as a tonic, so to speak, because the man was debilitated? There are many less expensive, more innocuous tonics.

The emotional lability in this patient during the last several days of June can be readily explained by his profound and prolonged illness. Who would not be emotionally unstable with such a prolonged, debilitating condition?

On June 29, the patient became jaundiced. This condition should be carefully considered. Why did he become jaundiced? Damage to the liver may occur from the administration of antibiotics, but chlorpromazine is a more important hepatotoxic agent. He received only 400 mg. of chlorpromazine; however, this is a sufficient amount to produce jaundice, a chlorpromazine hepatitis or a chlorpromazine intrahepatic cholangitis or cholestasis. As a matter of fact, 50 mg. of this drug is sufficient to produce these conditions. The duration of jaundice does not depend on the amount of chlorpromazine given; I saw one patient who received only 75 mg. and had a very profound and prolonged jaundice for which an exploratory laparotomy was seriously considered. The period between the administration of the drug and the onset of jaundice varies tremendously. Jaundice may occur within a few days or it may occur several weeks later. It is possible that chlorpromazine caused the jaundice in this patient. I am more concerned with the fact that blood transfusions were given within the incubation period of a homologous serum hepatitis.

Examination on June 30 disclosed a questionable mass in the periumbilical area, which is another problem to consider. We do not know whether the mass was hard, whether it was felt by several examiners, whether it moved with respiration, or whether it was tender. Was the jaundice in this patient caused by a neoplasm or was it due to an obstruction of the common duct? The spleen could not be palpated.

We have speculated that this patient may have had an intrahepatic cholestasis, a homologous serum hepatitis or a carcinoma; of these three, homologous serum hepatitis is most likely to produce splenomegaly. In chlorpromazine cholestasis, splenomegaly is uncommon, and it should not occur in obstruction of the common duct by a neoplasm unless the neoplasm also involves the splenic vein. However, this patient had no enlargement of the spleen. Of course, the spleen is palpable in only 10 to 25 per cent of patients with homologous serum hepatitis.

This patient was dehydrated and delirious. Was the delirium due to infection, which he had had for a long time, or was it due to a grave liver disease with a severe hepatocellular necrosis? A description of the delirium probably would have been helpful. A patient with liver disease does not go into delirium very abruptly. Somnolence and lethargy usually occur first, followed by disorientation and, finally, coma. Initially, this is a responsive coma from which the patient can be aroused by painful stimuli. Later, it becomes a deep coma from which the patient cannot be aroused. It also would have been helpful to know whether this man had either a flapping tremor or fetor hepaticus.

Convulsions are not commonly associated with liver failure. We must think of other possibilities to explain the convulsions in this patient. Did brain abscesses due to sepsis develop and cause the convulsions? If he had a tumor, did he have metastasis to the brain, which could have caused the convulsions?

DR. ISRAEL E. KIRSH (staff physician, radiology service): An x-ray of the pelvis showed changes usually seen with paraplegia, including the loss of bone substance, ossifications in the soft tissues adjacent to the hips, and densities in the bladder region, which were due to calculi. The chest films showed no abnormalities. It was reported that on one film some pneumonia was seen, but there was relatively little of a pathologic nature in that x-ray, and I probably would have said the findings were negative. Films of the gastrointestinal tract showed no evidence of ulcer and certainly no pyloric obstruction. There was thickening of the folds in the antrum, which was suggestive of antral gastritis rather than of a neoplasm.

DR. SPELLBERG: I agree with Dr. Kirsh that the x-rays did not demonstrate the presence of a gastric neoplasm. I do not think that the questionable mass was a gastric neoplasm or that there was any evidence of this condition.

I certainly would have liked to have had an electroencephalogram included in the laboratory studies. In the absence of other clinical evidence of hepatic failure, an electroencephalogram may show findings typical of hepatic coma and also serve to localize any other lesions in the brain.

There are some unusual findings in the laboratory reports. For example, a progressive jaundice developed in the patient on June 29. It is impossible to explain the absence of bile in the urine unless there was severe renal failure and the bile was not excreted. However, nonprotein nitrogen on July 1 was only 29, indicating that the excretory capacity of the kidneys was good. A faint trace of urinary urobilinogen was reported on June 30. The urobilinogen might have been absent if there had been a complete obstruction, either intrahepatic or extrahepatic. Now, the direct bilirubin was 3.5 mg. and the indirect bilirubin was 2.9 mg., giving a total of 6.4 mg., which is enough to give a lot of bile in the urine. The report of the absence of bile in the urine must have been a laboratory error.

Results of the other liver function tests are important. The precipitous drop in the serum albumin within a period of about six weeks indicated severe hepatocellular damage. The amylase was normal, and alkaline phosphatase was 11.4 Bodansky units. The latter is of some importance, because I would expect a patient dying from severe hepatocellular necrosis to

have a lower alkaline phosphatase. Perhaps he died so quickly that there was still elevation of the alkaline phosphatase. The thymol turbidity of 13 and the cephalin-cholesterol flocculation of 4 plus at 48 hours indicate hepatocellular damage. I do not believe that this patient had a carcinoma obstructing the common bile duct, because this would not produce the abnormal flocculation test results or the rapid fall of the serum albumin. For these same reasons, I do not believe he had a chlorpromazine cholestasis.

The most likely possibility is that this patient had a homologous serum hepatitis, although we also must consider the possibility of pylephlebitic abscesses of the liver. Pyogenic liver abscesses usually will produce a severe leukocytosis. This patient had a white blood cell count of only 14,800 on July 2. From the data given, I would conclude that he had a homologous serum hepatitis with severe liver necrosis, an infection of the urinary tract, probably with bilateral pyelonephritis, and possibly a hematogenic spread of the infectious process.

DR. ARMAND LITTMAN (chief, medical service): I would like to comment on two of the conditions found in this patient, Dr. Spellberg. There certainly is no question that patients with urosepsis may have tremendous transfusion requirements. In addition to urosepsis, this patient had chronically infected decubitus ulcers. Surgeons regard blood as something more than a tonic. I think they consider that a normal hemoglobin level is essential to the healing of decubitus ulcers.

DR. SPELLBERG: I did not mean to be overly critical in regard to the blood transfusions. I similarly transfuse patients with chronic ulcerative colitis. However, this patient had hemoglobin levels which were persistently near normal.

DR. RALPH PACINI (assistant chief, gastroenterology section): Dr. Spellberg, would you consider pancreatitis in view of the abdominal mass, the pneumonitis on the left side, and the general course?

DR. SPELLBERG: There were no symptoms of pancreatitis. The patient had an amylase of only 39 units and no abdominal rigidity, tenderness or pain. The rapidly progressive jaundice and the rapid deterioration evidenced by the results of the liver function tests make me believe that this was hepatocellular disease.

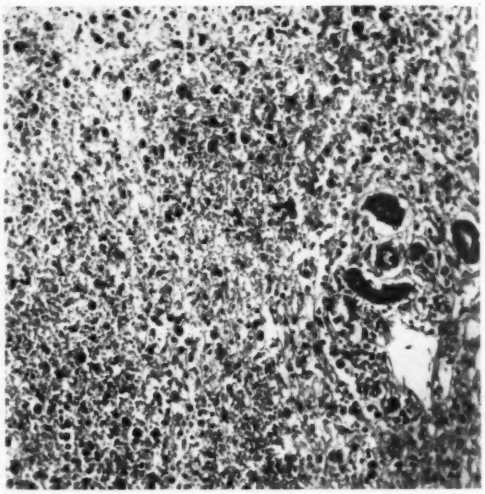

FIGURE 1. Photomicrograph of the liver, showing complete necrosis of liver cord cells with remaining bile ducts enmeshed in a fine reticulin network.

DR. MYRON E. RUBNITZ (chief, laboratory service): As indicated by Dr. Spellberg, this patient had a severe acute necrosis of the liver due to serum hepatitis. The liver was approximately one-half the normal size and weighed about 800 gm. In some areas the liver was a yellowish color, but it showed the reddish and gray areas more typically seen in acute necrosis of the liver.

Microsections of the liver showed many areas in which there were only a few isolated bile duct structures surrounded by a network of reticulin fibers, macrophages and inflammatory cells (figure 1). Persistence of the reticulin is characteristic of viral hepatitis and permits regeneration in less severe cases. Only a few regenerating areas were present in this case. Some of the liver cord cells showed fat vacuoles, although these are not usually found in serum hepatitis.

Of course, this patient showed the results of the long-standing paraplegia, with the muscle atrophy and the decubitus ulcers described in the protocol. In the peritoneal cav-

ity there was 500 cc. of yellow ascitic fluid. The lungs showed a bilateral bronchopneumonia of the lower lobes. The spleen weighed 350 gm., which is about two and a half to three times the normal size. Esophageal varices were grossly visible, an unusual finding in acute or subacute liver disease without cirrhosis.

DR. SPELLBERG: I would like to make one more point. In any chronic illness, especially of the type that this man had, there may be some evidence of liver disease. This patient showed fatty metamorphosis of some of the liver cells, probably antedating the serum hepatitis. This may have been one of the reasons why he had such a rapid downhill course, with a fulminant hepatitis terminating in death within four days. The fact that the liver could not be palpated was indicative of its rapid decrease in size.

Dr. Rubnitz told us that the spleen actually was enlarged. If you cannot feel the spleen, you must try to percuss it. A definite increase in splenic dullness is a valuable finding when the spleen cannot be felt.

Books Received

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Reviews appear in this issue starting on page A-141.

An Atlas of Acquired Diseases of the Heart and Great Vessels. By Jesse E. Edwards, M.D., Professor of Pathology, Mayo Foundation, Rochester. Vols. 1, 2 and 3. 1,401 pages, illustrated. 1961, W. B. Saunders Company, Philadelphia and London. $70.00.

711 Medical Maxims. By William S. Reveno, M.D., Wayne State University College of Medicine, Detroit. Vol. 2. 177 pages. 1961, Charles C Thomas, Springfield, Illinois. $3.50.

Enzymology in the U. S. S. R.; a Review of the Literature. By Chester W. De Long, Ph.D. Public Health Service Publication No. 782. 189 pages. 1960, Public Health Service, U. S. Department of Health, Education, and Welfare. $0.65.

Handbook of Surgery. Edited by John L. Wilson, M.D., Veterans Administration Hospital, San Francisco, and Joseph J. McDonald, M.D., American University of Beirut School of Medicine, Beirut, Lebanon. 647 pages, illustrated. 1960, Lange Medical Publications, Los Altos, California. $4.00.

The Air We Breathe. A study of man and his environment. Edited by Seymour M. Farber, M.D. and Roger H. L. Wilson, M.D., University of California School of Medicine, Berkeley-San Francisco. 414 pages, illustrated. 1961, Charles C Thomas, Springfield, Illinois. $14.00.

Medical Almanac 1961-62. Compiled by Peter S. Nagan, M.S., Washington, D. C. 528 pages. 1961, W. B. Saunders Company, Philadelphia and London. $5.00.

Mathematical Biophysics; Physico-mathematical Foundations of Biology. By N. Rashevsky, Professor and Chairman, Committee on Mathematical Biology, University of Chicago, Chicago. Ed. 3. Vols. 1 and 2. 950 pages, illustrated. 1960, Dover Publications, Inc., New York. $5.00.

Progress in Medical Virology. Edited by E. Berger, Basel, Switzerland, and J. L. Melnick, Houston, with 10 contributors. Vol. 3. 496 pages, illustrated. 1961, Hafner Publishing Company, Inc., New York. $20.50.

Radiopaque Diagnostic Agents. American Lecture Series. By Peter K. Knoefel, M.D., Professor of Pharmacology, University of Louisville School of Medicine, Louisville. 157 pages, illustrated. 1961, Charles C Thomas, Springfield, Illinois. $6.75.

From Girlhood to Womanhood. By Albert Sharman, M.D., Glasgow, Scotland. 72 pages. 1960, E. & S. Livingstone Ltd., Edinburgh and London. Distributed by The Williams & Wilkins Company, Baltimore. $1.75.

Chest Pain; Systematic Differentiation and Treatment. By Nathaniel E. Reich, M.D. and Rudolph E. Fremont, M.D., State University of New York Downstate Medical Center, Brooklyn. 366 pages, illustrated. 1961, The Macmillan Company, New York. $9.00.

A Biochemical Basis of Multiple Sclerosis. American Lecture Series. By Roy L. Swank, M.D., Professor and Head, Division of Neurology, Department of Medicine, University of Oregon Medical School, Portland. 88 pages with 14 illustrations. 1961, Charles C Thomas, Springfield, Illinois. $5.00.

Recent Advances in Human Genetics. Edited by L. S. Penrose, M.D., Galton Professor of Eugenics, University College, London, England, with seven contributors. 194 pages with 13 illustrations. 1961, Little, Brown & Company, Boston. $8.00.

Emotional Problems of the Student. By Graham B. Blaine, Jr., M.D., Psychiatrist, and Charles C. McArthur, Ph.D., Psychologist, University Health Services, Harvard University, Boston, with 14 contributors. 254 pages. 1961, Appleton-Century-Crofts, Inc., New York. $4.95.

Synopsis of Oral Pathology. By S. N. Bhaskar, Ph.D., Chief, Oral Tumors Branch, Armed Forces Institute of Pathology, Washington, D. C. 502 pages with 325 illustrations. 1961, The C. V. Mosby Company, St. Louis. $9.75.

Self-help Devices:

Homemaking: Kitchen Area Safety Measures

EDWARD W. LOWMAN AND HOWARD A. RUSK

Institute of Physical Medicine and Rehabilitation
and the Arthritis Self-help Device Office*

New York University Medical Center, New York

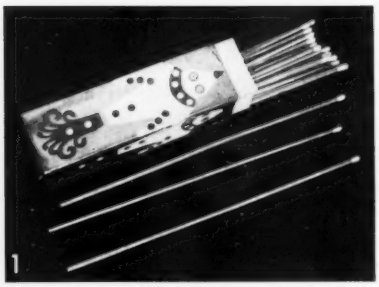

FIGURE 1. Lighting a gas stove not equipped with an automatic pilot is a source of danger to the disabled homemaker, particularly if she is confined to a wheel chair. Long wooden matches of fireside or barbecue length or a taper will compensate for her limited reach and will keep her hand from the immediate proximity of the flame.

FIGURE 2. The patient who is unable to bend can manage a low oven by holding the long match with a pair of wooden scissor tongs. A hand mirror with a long handle can be used as a reflector in checking the jets during lighting and foods while cooking. A mirror placed over the stove will aid the wheel-chair patient in checking the progress of foods cooking on top of the stove.

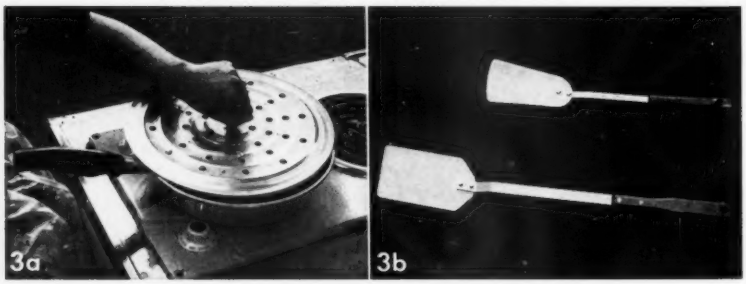

FIGURE 3. Spattering grease or steam can cause severe burns, particularly to the homemaker sitting at a height that is level with the stove. Spatter lids (a) and oversized utensils of barbecue length (b) prevent this danger.

A whistling teakettle with its permanent cover and easily triggered spout opening is safer to use than one with a removable lid. The spout of any teakettle should always face the rear of the stove.

*Supported at the Institute by the Arthritis and Rheumatism Foundation.

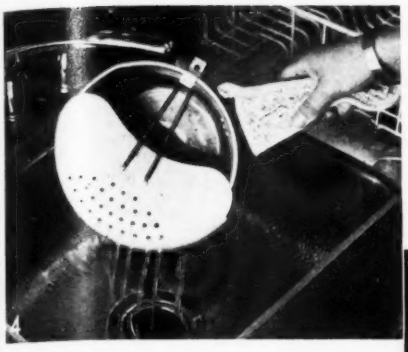

FIGURE 4. Strainer lids, which are put on the pan before it is placed on the stove, make possible the safe drainage of hot liquid. These lids are especially useful to persons who must work with one hand.

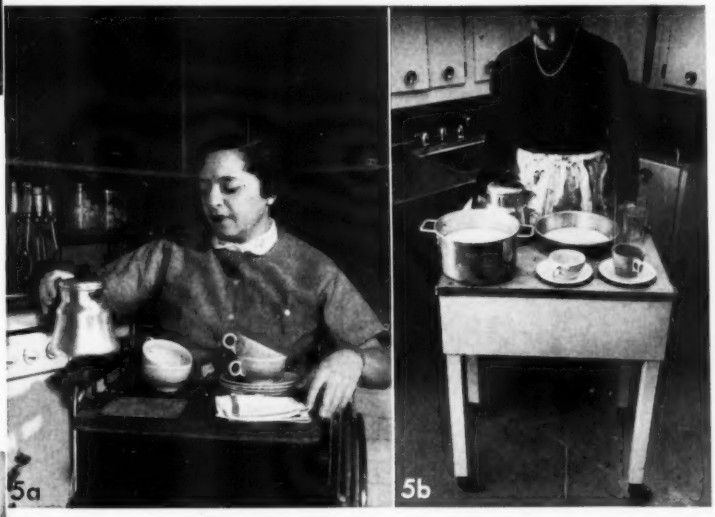

FIGURE 5. Persons confined to a wheel chair will find a lapboard (a) or tray convenient for transporting hot containers from the stove to other areas. The ambulatory patient will manage well with either a wheeled table (b) or a cart.

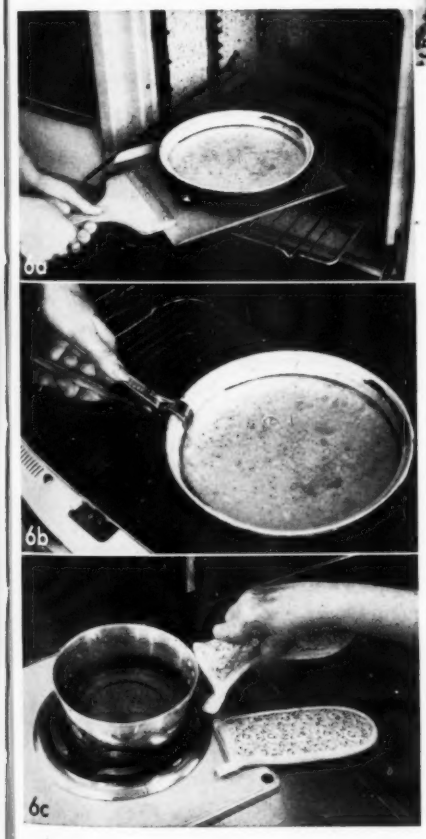

FIGURE 6. The Oven Shovel (a) and grippers (b) increase reach and eliminate the need for direct handling of hot containers. Fitted glovelike pot holders (c) are perhaps safer than other types of holders.

FIGURE 7. If a container is too heavy to lift safely, it is often wise to ladle off some of the contents before attempting to move it.

Editorials

Postgraduate Medicine

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PROPRIETARY NURSING HOMES

As a part of the Health Information Foundation research series, a report has just appeared based on interviews with the operators of 35 nursing homes in Detroit. Most of these are housed in old buildings not originally designed to be nursing homes. The situation in Detroit is undoubtedly duplicated in other large cities in the United States. Briefly, the beds are needed; time has not permitted the necessary construction of many buildings designed specifically as nursing homes. Hence, old houses are used, since these may be had at reasonable cost, having been sold by owners who were unable to secure adequate domestic help.

These proprietary nursing homes do not have an adequate number of nurses and other nursing personnel, and they certainly lack specially trained geriatric nurses. Indeed, most nurses find the care of the aged unpleasant and without the emotional reward of cures. Specifically lacking are persons capable of aiding in rehabilitation of the aged; most homes cannot afford such personnel. The report showed that three homes had cooperated in employing an occupational therapist; however, at the end of one year, the results were characterized as "very poor." Seldom is a physician employed on a full-time basis, but, in most instances, one or two physicians are available on call. Some families retain their family physician, who makes periodic visits to the nursing home.

The whole picture seems to reflect the fact that governmental institutions are large and imposing but not particularly attractive to the aged. The homes conducted by nonprofit churches and fraternal groups vary in size, but the tendency is toward a large number of beds. Most proprietary nursing homes are small (25 or 30 beds) and limited by the capital investment available. However, these smaller proprietary nursing homes do not qualify as having "homelike" qualities.

In Michigan, the State Department of Health licenses and regulates proprietary nursing homes. Faced with the difficulty of the current situation, this department has recognized the necessity for gradual adjustment in standards. The difficulties of inspection are tremendous because the status of proprietary nursing homes is low in the health community. Those who conduct them have avoided any active role in community health planning.

The study by the Health Information Foun-

dation was aroused by strong hints that something sinister would be found in private nursing homes. They are frequently called "terrible" or "miserable." The investigators in Detroit do not believe that conditions are bad enough to warrant the unfair opinions that are held, but they recognize the great necessity for improvement. Many nursing homes are conducted as businesses, with the hope of large profits, and the prospect that speculators will increasingly enter the field is likely. The profits seemed, however, much smaller than many believe. Actually, those who conduct the homes are seldom qualified in regard to knowledge of what constitutes good medical and personal care. The nurses believe that the ignorance shown by administrators is actually depriving patients of the benefits of new drugs and new methods of treatment. They feel that minimal care is usually given. Apparently, the quality of the care is determined by its cost. It is likely that rehabilitation will not be attempted on any large scale and that such efforts are beyond the capacity of those caring for the patients.

Seventy-one per cent of the operators interviewed believe that the number of proprietary nursing homes will increase and that they will become capable of meeting increased needs. Nevertheless, anticipation is high that both local and federal governments will take an increasing part in housing and in caring for aged persons. The anticipation of governmental entrance into the field lessens the likelihood of increased investment by owners of proprietary nursing homes.

MORRIS FISHBEIN

EASY MONEY

ACCORDING to The Foundation Directory,[1] the people of the United States now have 12,202 foundations with assets approximating $11,613,000,000. The vast funds available from the Ford, Rockefeller and Carnegie Foundations are now supplemented not only by many smaller agencies but also by the giant of them all, the government of the United States.

Mr. John M. Russell, president of the John and Mary R. Markle Foundation, in his annual report expresses alarm at the rapidity with which thoughtful people who feared federal aid to medicine in the past have shifted position and now lend their names in support of Congressional action leading to well-nigh unlimited money for medical research. "The reason is," he says, "that the medical schools for the first time have had a taste of easy money." Now they are actually being asked to apply for grants. "At long last, money—big money—is available, or soon will be, to pay for top research workers and faculty members, and for buildings, equipment and all sorts of delectable things their mouths have watered for these many years."

The tremendous response of the Congress in voting funds is, Mr. Russell believes, the result of emotional interest in health matters. The private foundations support ideas and projects of great value without emotional appeal. While government can support the unemotional, the representatives of a people cannot ignore their interests and their demands. Mr. Russell notes that the Congress regularly cuts the requested budget for the National Science Foundation, which acts like a private foundation, and vastly increases the budget of the National Institutes of Health, which, he says, "is bursting with emotions." He sees a great hazard in the realization by great numbers of exploiters that the Congress can be reached through such emotional demands.

The big danger in federal aid to medical education is this possibility of an emotional rather than a scientifically justified appeal. Easy money makes for careless spending.

MORRIS FISHBEIN

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PROBLEMS OF MATERNITY

MATERNAL mortality usually is given as the number of maternal deaths per 10,000 live births. Different areas of the United States

have for many years recorded widely different maternal mortality, varying from as high as 31.4 in Mississippi in 1946 to 9.2 in Connecticut. The rates obviously are related to the status of maternal care in childbirth, the nature of the population, and many other factors.

During the years from 1933 to 1948, maternal mortality in the United States was reduced approximately 80 per cent. Rates have continued to fall. In the past, the major terminal causes of maternal deaths have been hemorrhage, infection and the toxemias of pregnancy, which accounted for approximately 90 per cent of the total. Other causes are such conditions as heart disease, accidents under anesthesia, and similar problems.

In the enlightening publication *Patterns of Disease*, published and circulated to the medical profession by Parke, Davis & Company, attention is called to the possibility that the woman's attitude toward her pregnancy may influence her physical condition. A survey showed that emotions may play some part in the development of toxemia, although this is not fully established scientifically. This study showed that 57 per cent of those in whom toxemia developed pitied themselves and women in general, while this feeling did not prevail among patients in whom this complication did not develop. Also, according to the same survey, 77 per cent of patients with toxemia felt guilt toward their unborn babies, and 70 per cent associated pregnancy with deceit, shame or sin; these attitudes were present in only about 7 per cent of healthy women.

The lowest mortality from complications of pregnancy is among women between ages 20 and 24; highest is among those over 45. The mortality of pregnant teen-agers is 2.5 for every 10,000 live births. The rate falls to 1.9 among those in the early 20s and then rises from three in the late 20s to 5.4 in the early 30s, 9.1 in the late 30s, 13.3 in the early 40s, and 23.5 in the group over 45. Of maternal deaths, 24 per cent are caused by toxemia, 17 per cent by hemorrhage, and approximately 10 per cent by abortion with sepsis. In a study of births among 1500 teen-age mothers, a correlation was found between weight gains of 40 lb. or more and the incidence of eclampsia.

A survey just made available by the Health Information Foundation reveals that women who were delivered of a viable infant during 1957 and 1958 sought medical care earlier in pregnancy and used more physician's services than did expectant mothers five years previously. Expenditures on maternity care during 1957 and 1958 constituted about 6 to 7 per cent of the gross total private expenditure for health, with an average expenditure for a confinement of about $272. The survey showed that there has been a continuous increase in expenditures involving health services for maternity care, in the amount of private expenditure for these services, and in the insurance benefits to cover the expenditure. A significant increase has occurred in the frequency of early consultation with a physician, the average number of prenatal visits, and the use of hospitals at delivery.

The increase in expenditure for confinement from $193 in 1952 to $272 in 1957 is associated with the great increase in the proportion of births that occur in the hospital. If hospital births only are considered, the increase has been only from $213 to $274. Incidentally, the average stay in the hospital for delivery actually decreased between 1952 and 1958. The proportion of women who stayed seven or more days dropped from 17 to 10 per cent, and the proportion who stayed eight or more days dropped from 7 to 5 per cent. The average time in the hospital after delivery is now from 4.5 to 4.7 days.

The information derived from these studies is proof-positive that the great advances which have been made in medical science, such as the use of blood transfusions in hemorrhage, the use of antibiotics to control infection, the practice of asepsis in obstetric care with deliveries in hospitals, and the improvement in nutrition and medical care generally, are definitely reflected in decreased morbidity, shortening of hospital stay, and lower maternal mortality.

MORRIS FISHBEIN

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DESCRIPTION: Employing the completely integrated MicroZoom optical system, this line of microscopes has a continuous magnification range extending from 17.5 to 1,940x. Features include a single eyepiece which provides 1 to 2x magnification; six interchangeable bodies, each fully rotatable through 360 degrees on a common arm bracket; inclined eyepiece tubes; an automatic interpupillary distance adjustment; coated aluminum mirrors with enhanced reflectivity; color-coded 10x, 43x and 97x objectives; ball-bearing movements controlling the nosepiece and stages; a circular 148 mm. diameter glide stage; and a closed-type base which provides firm support for illuminator accessories. Attachments for 35 mm. cameras and POLAROID® Land Cameras are available for models that are adapted for photomicrography.
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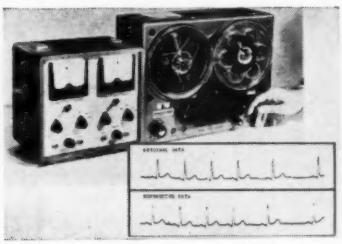

• TAPE RECORDER (Model 102A)

DESCRIPTION: Designed for recording electrocardiographic and electroencephalographic data and for medical and biologic research, this portable two channel tape system provides 0.2 per cent precision in recording and reproducing all analog data from 0 to 400 cycles. It features a standard tape transport, three tape speeds, wide dynamic range, independent recording and reproduction channels, and low noise and cross-talk levels.
PRODUCER: Mnemotron Corp., Spring Valley, N. Y.

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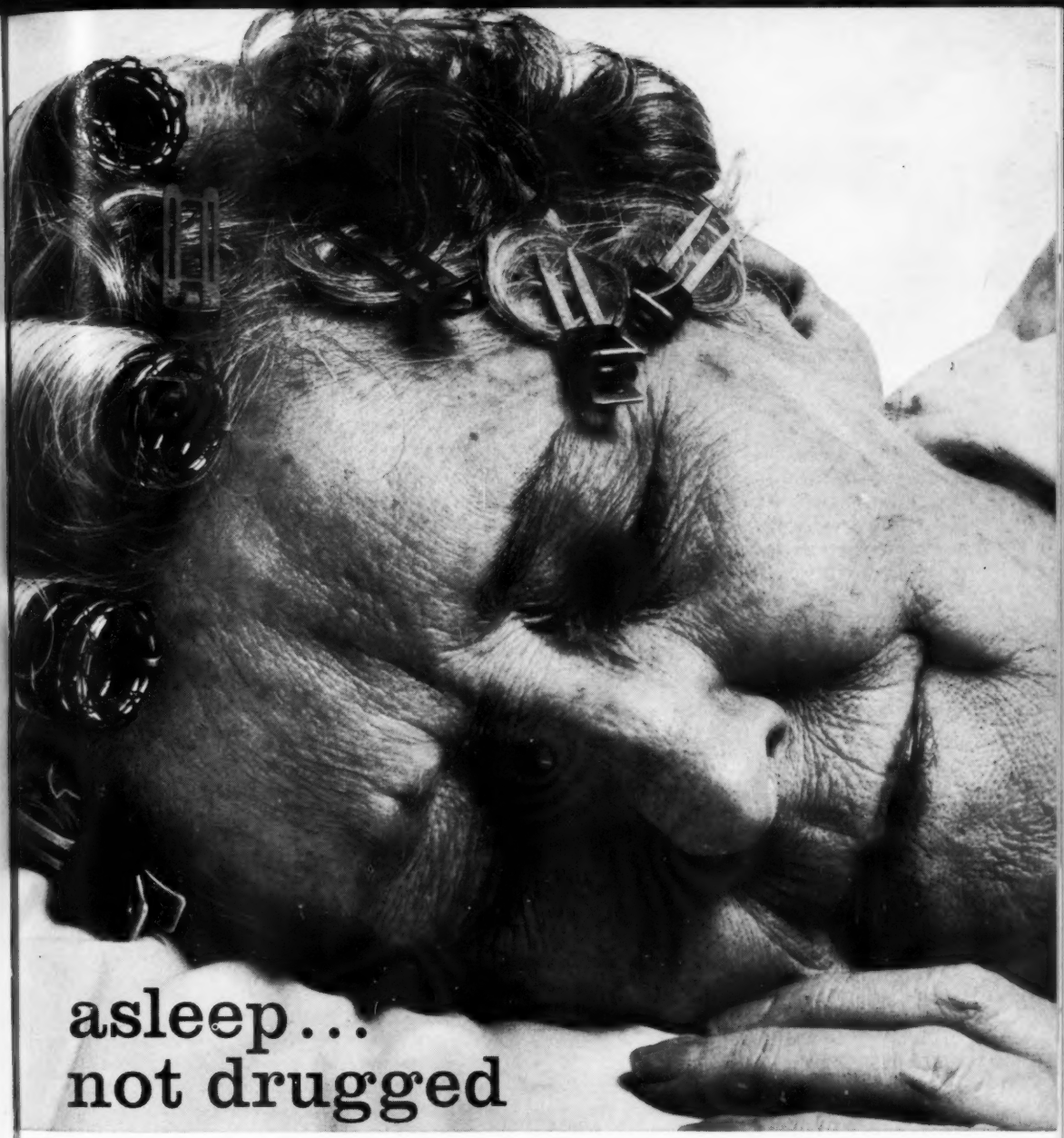

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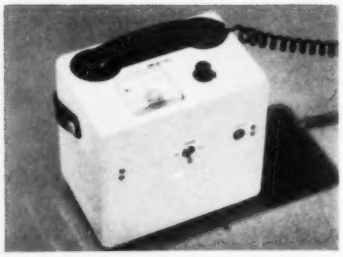

• MEDI-TEL
(Model 613 M)

DESCRIPTION: Consisting of a transmitter and a receiver, this system is designed on the basis of standardized telephone telemetering technics and can transmit recorded electrocardiogram signals to diagnosticians at remote locations. From the transmitter, controlled low-frequency FM signals carry electrocardiogram signals over a landline data link to the receiver, which reproduces them for remote analysis. The transmitter is adapted to fit most amplifying types of electrocardiographs.
PRODUCER: Electro-Medical Engineering Company, Inc., Burbank, Calif.

• ZENTRON®

PURPOSE: To correct iron deficiency.
COMPOSITION: Each 5 cc. contains 100 mg. ferrous sulfate plus seven vitamins and 2 per cent alcohol.
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PRODUCER: Eli Lilly and Company, Indianapolis.

• UN-TEST

DESCRIPTION: Used for the colorimetric quantitation of urea nitrogen, this test eliminates boiling and the need for elaborate apparatus. Color intensities are reproducible within 1 per cent, and the high reaction sensitivity permits an assay of only 0.02 ml. serum without deproteinization. Materials come in compact kits, each containing 20 ml. dried buffered urease, 5 gm. concentrated phenol color reagent, and 14 ml. concentrated alkali-hypochlorite reagent.
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DOSAGE AND ADMINISTRATION: 1 Dura-Tab before breakfast.
HOW SUPPLIED: Bottles of 30, 100 and 250.
PRODUCER: Wynn Pharmacal Corp., Philadelphia.

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PRODUCER: Sanborn Company, Waltham, Mass.

(Continued on page A-111)

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In pharmacologic studies at Pasteur Institute and McGill University, the vasodilator activity of trolnitrate phosphate (METAMINE) was found to be equal or superior to that of nitroglycerin, and of much longer duration.[1-2]

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1. Bovet, D., and Nitti-Bovet, F.: Arch. Internat. de pharmacodyn. et therap. 83:367, 1946. 2. Melville, K.I., and Lu, F.C.: Canad. M.A.J. 65:11, 1951. 3. Fuller, H.L. and Kassel, L.E.: Antibiotic Med. & Clin. Therapy 3:322, 1956. 4. Elsfelder, H.W. et al.: J. Am. Geriatrics Soc. 8:62, 1960.

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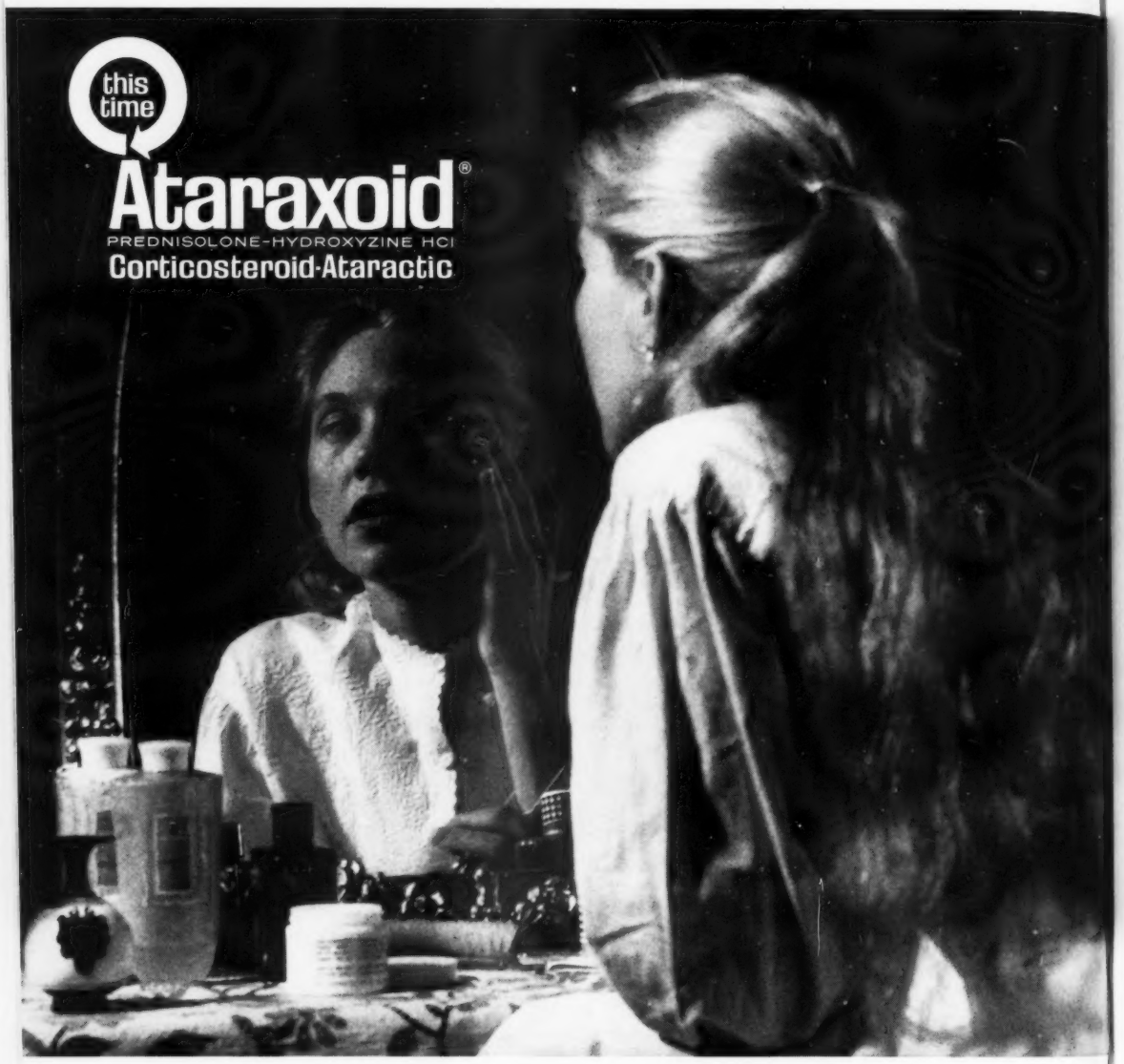

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1. Brown, E. B., and Seideman, T.: J. Allergy 29:80, Jan., 1958.

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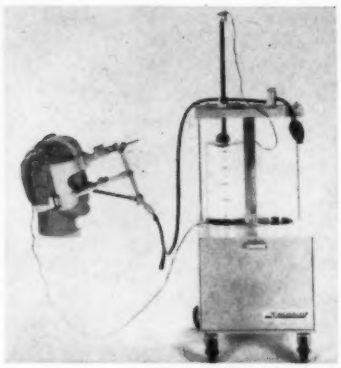

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DESCRIPTION: For emergency management of gastroesophageal varices in portal hypertension, this device includes an automatic balloon tamponade and a control apparatus. The latter consists of two synchronized elements provided with separate alarm systems. A headgear maintains the nasogastric tubes in position and measures the direct traction on the gastric balloon on a 1600 gm. scale. An air reservoir with a parallel standpipe controls intraesophageal balloon pressure and supplies the gastric balloon with air. Should pressure drop or the balloon deflate, one of the two alarm signals is set off, but neither signal is activated by normal sudden contractions of the diaphragm.
PRODUCER: Air-Shields, Inc., Hatboro, Pa.

• **ALDACTAZIDE®**

PURPOSE: Diuretic therapy.
COMPOSITION: Each tablet contains 75 mg. spironolactone (ALDACTONE®) and 25 mg. hydrochlorothiazide.
CAUTION: This drug should be administered with caution to patients with severe hepatic disease. Hyponatremia, hyperpotassemia, hyperuricemia, hepatic coma, gastrointestinal intolerance, and hypersensitivity reactions to the individual components of this drug may develop.
DOSAGE AND ADMINISTRATION: For adults the usual dosage is 1 tablet four times daily but may range from 1 to 8 tablets daily; for children, the daily dosage should provide 3 to 6 mg. Aldactone per pound of body weight.
HOW SUPPLIED: Bottles of 20 and 100 tablets.
PRODUCER: G. D. Searle & Co., Chicago.

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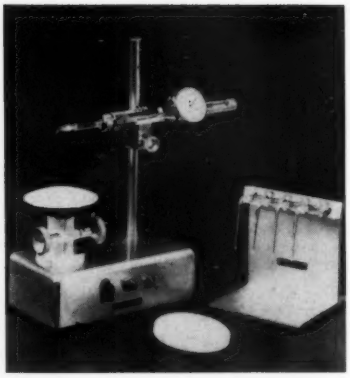

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DESCRIPTION: For use in the clinical laboratory where microdeterminations are required, this device can make aliquots as small as 0.001 ml. It combines a precision micropipet with a magnetic stirrer of adjustable height. The magnetically driven turntable rotates beakers and test tubes for pipet tip stirring. A unique zeroing mechanism permits direct reading of aliquot volumes from the dial face. Each instrument is furnished with a separate mounting rack and five interchangeable reagent reservoirs of 0.1 and 1.0 ml. capacities.
PRODUCER: McDonald Instrument Company, Cleveland.

• NORLUTATE

PURPOSE: To treat disorders of menstruation and pregnancy that are associated with progesterone deficiency.
COMPOSITION: Each tablet contains 5 mg. norethindrone acetate.
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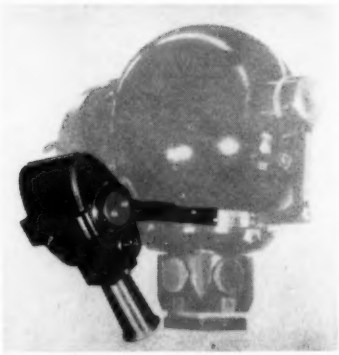
DOSAGE AND ADMINISTRATION: 1 or 2 capsules three times a day.
HOW SUPPLIED: Bottles of 50.
PRODUCER: Roche Laboratories, Division of Hoffmann-La Roche, Inc., Nutley, N. J.

• HALDRONE®

PURPOSE: Corticosteroid therapy.
COMPOSITION: Paramethasone acetate.
CAUTION: The usual contraindications to corticosteroid therapy apply to Haldrone.
DOSAGE AND ADMINISTRATION: Dosage should be individualized for each patient.
HOW SUPPLIED: 1 or 2 mg. tablets in bottles of 30, 100 and 500.
PRODUCER: Eli Lilly and Company, Indianapolis.



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PRODUCER: Picker X-Ray Corporation, White Plains, N. Y.

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PURPOSE: To treat vaginitis.
COMPOSITION: Each 5 cc. vial contains a minimum of 200,000 lyophilized, viable bacilli in a preparation to be reconstituted with sterile distilled water.
DOSAGE AND ADMINISTRATION: Insert the reconstituted contents of 1 vial once every three days until growth of Döderlein's bacillus is established.
HOW SUPPLIED: Packages of six.
PRODUCER: Testagar & Co., Inc., Detroit.

THE MEDICAL Bookman

► HENRY STANLEY PLUMMER
A Diversified Genius

By Fredrick A. Willius, M.D., formerly Head, Section on Cardiology, Mayo Clinic, Rochester, Minnesota. 71 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $4.50.

Henry Stanley Plummer was a man of infinite variety. His career was Minnesota all the way. He was born in Hamilton, Minnesota, and graduated from the local schools. After two years in the University of Minnesota, he attended Northwestern University Medical School, Chicago, receiving his M.D. in 1898. His early leanings were toward engineering, but his medical father and paternal grandfather pushed him into medicine. His enrollment in the Mayo Clinic was a result of a casual contact with Dr. William J. Mayo, who had been called in consultation by Dr. Albert Plummer.

Dr. Plummer was associated early in his career in Rochester with E. Starr Judd, Braasch, Balfour, Henderson and many others. His bent toward engineering led him to early use of the x-ray, to the building of devices for use in the esophagus and the stomach and for measuring hypertension, and into early contact with electrocardiography. With Boothby, he pioneered in the development of the use of oxygen and the apparatus for that purpose. His genius for engineering made him the leader in the building of the great Mayo Clinic building of 1929, which is known today as the Plummer Building.

Dr. Plummer's genius and intellect contributed so greatly to the heights achieved by the Mayo Clinic and the Mayo Foundation that they will be remembered for many years to come. This was a man who lived largely in his mind. He read widely, but perhaps with difficulty; yet, he surmounted his eccentricities and his peculiarities in a triumphant contribution to many engineering and mechanical aspects of medical progress.

M. F.

► PEDIATRIC X-RAY DIAGNOSIS

By John Caffey, M.D., Director of Medical Education, Children's Hospital of Denver, Denver. Ed. 4. 1,236 pages with 1,536 illustrations. 1961, Year Book Medical Publishers, Inc., Chicago. $32.00.

In 15 years and three editions, Dr. Caffey's text on pediatric radiology has become an American classic. It was begun at the Babies' Hospital, New York, and now has been moved to the Children's Hospital of Denver.

The differences between previous editions and this greatly enlarged edition are so well set forth in the author's preface that it is unnecessary to restate them here in detail or to add to the author's admonition that one should avoid both needless radiation of children and failure to make x-rays when x-rays are of vital importance in diagnosis.

An authoritative textbook in any branch of medicine must be so large that it will scarcely ever be read from cover to cover. If it is a grade A textbook, it will have such complete, well-indexed and well-illustrated coverage that a reader desiring dependable information on any phase of the subject may turn to it, confident that his question will be answered. Dr. Caffey's book qualifies richly as a grade A textbook. It is a credit to its publisher and to its author and his numerous associates. It also emphasizes the fact that in American medicine of 1961 superannuation and technical retirement need not interrupt or terminate one's usefulness to society.

P. C. H.

(Continued on page A-144)

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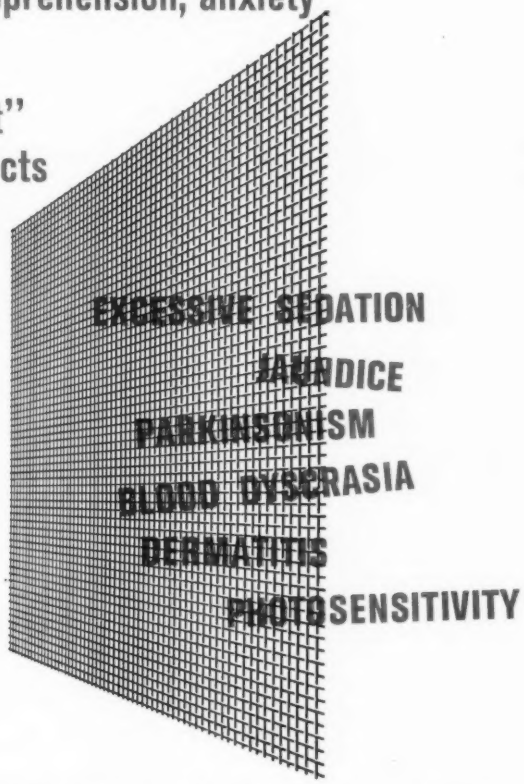

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1. Sandison, R. A., Whitelaw, E., and Currie, J. D. C.: Clinical trials with Mellaril in the treatment of schizophrenia, Journal of Mental Science (British Journal of Psychiatry) 106:732, April, 1960. 2. Freed, S. C.: Thioridazine, a neuroleptic in general practice, International Record of Medicine, 172:644, Oct. 1959.

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With medical literature concentrating on curing disease, the problem of how to give relief for the patient's symptoms usually receives scant attention. On the other hand, the advertising pages of our medical journals are often filled with somewhat indiscriminate recommendations for the use of drugs for the relief of symptoms and prescriptions for making the patient feel better.

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► THE YEAR BOOK OF DRUG THERAPY (1960-1961)

Edited by Harry Beckman, M.D., Chairman, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, Milwaukee. 587 pages with 57 illustrations. 1961, Year Book Medical Publishers, Inc., Chicago. $8.50.

This fully indexed volume presents to the physician a truly clinical drug-consultation service. As usual, Dr. Beckman has enhanced the book with his own excellent editorial comments.

The blue page section, introduced last year, has a very fine discussion on the bases for judging a new drug, including method of production, need for the drug, a comparison of cost and therapeutic value, side effects, and contraindications. New drugs of the past year are discussed.

The remainder of the volume covers 456 new or improved treatment measures, 57 of the latest diagnostic procedures, 66 case reports, 128 informative clinical studies, and practical new therapeutic approaches to 293 conditions. The discussions of various drugs for many conditions represent abstracts of 504 pertinent articles on current drugs and their application in general practice and the specialties.

I. P. F.

► RADIATION THERAPY OF EARLY PROSTATIC CANCER

By R. H. Flocks, M.D. and D. A. Culp, M.D., Department of Urology, State University of Iowa College of Medicine, Iowa City. American Lecture Series. 73 pages, illustrated. 1960, Charles C Thomas, Springfield, Illinois. $4.50.

The first half of this short monograph is a historical review of the methods and results of the uses of radium in treating cancer of the prostate up to 1930. The reasons for using radiocolloid in 1950 are discussed, as well as the findings on the early series of patients treated by this means. The latter half of the book deals with the technics and methods of administering colloidal gold to patients, with a practical discussion of measures used to protect the personnel from radiation. The last chapter presents the results of 785 procedures performed on 517 patients.

D. S. C.

(Continued on page A-146)

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► HEART SOUNDS AND MURMURS A Clinical and Phonocardiographic Study

By P. A. Ongley, M.D., Consultant in Pediatrics, Mayo Clinic, Rochester, Minnesota, Howard B. Sprague, M.D., Board of Consultation, Massachusetts General Hospital, Boston, M. B. Rappaport, E.E., late Head of Department of Electrophysiologic Research, Sanborn Company, Waltham, Massachusetts, and A. S. Nadas, M.D., Cardiologist, Children's Hospital, Boston. 360 pages with 211 illustrations. 1960, Grune & Stratton, Inc., New York and London. $9.75.

The result of the collaboration of four distinguished authorities in the field of phonocardiography, this monograph is divided into four sections and includes a brief history of auscultation and the stethoscope. The clinical application is well done. The material is well chosen, well organized and excellently presented. The format is good and the illustrations are satisfactory. Those interested in the phenomena of heart sounds and murmurs will find that this book is well worth reading.

J. F. B.

► FRENCH'S INDEX OF DIFFERENTIAL DIAGNOSIS

Edited by Arthur H. Douthwaite, M.D., Senior Physician, Guy's Hospital, London, England. Ed. 8. 1,111 pages with 774 illustrations. 1960, The Williams & Wilkins Company, Baltimore. $24.00.

The rapid advances and changes in medical knowledge that have characterized the nearly half century since the original publication of this book accentuate the difficulties attending any attempt even to index current medical thought. Revisions of books of this type are seldom complete, and much that is antiquated remains to add volume and presumably expense to an already unwieldy tome. The perpetuation of atavistic ideas having little clinical or scientific foundation is unlikely to improve medical practice. To some degree, many sections of this book may be criticized on this basis. Even more deplorable are certain unacceptable statements. It is not generally accepted, for example, that carcinoid heart disease arises from secondary deposits in the pulmonary and tricuspid valves (p. 293) or that hepatic disease is seldom evident during life in patients with hepatolenticular degeneration (p. 319).

Excellent photographs illustrate many of the brief summaries of disease states. This book may be of value to the busy practitioner confronted with a puzzling symptom complex. It also may be of some use to any physician as a reference. The intent of the book, however, obviously is not to present detailed accounts of disease entities.

W. T. F.

► LEHRBUCH DER INNEREN MEDIZIN

Edited by Helmut Dennig, M.D., Stuttgart, with 12 contributors. Ed. 5. Vols. 1 and 2. 1,897 pages, illustrated. 1961, Georg Thieme Verlag, Stuttgart, Germany. Distributed in the United States and Canada by Intercontinental Medical Book Corporation, New York. $12.85 each volume.

The necessity of a fifth edition a few years after its first publication and its translation into Italian, Spanish and Polish speak for the wide and favorable acceptance of this textbook. Written by German authors, it covers the entire field of internal medicine and includes a general discussion on diagnosis and treatment of diseases in this field.

Each chapter presents the clinical picture of a disease, with brief descriptions of appropriate laboratory procedures and comments on pathophysiology and medical history. Following the modern trend, the discussion on congenital heart diseases is presented in rather great detail. On the other hand, problems related to fluid and electrolyte balance should have received more attention.

Both volumes are heavily illustrated; much of the illustration is done in color and most of it is very instructive and of excellent quality. The chapter on neurology deserves particular mention in this respect.

The physician with an adequate knowledge of German, especially if he is interested in thought and comment not commonly employed in the American literature, may find this book stimulating reading in many ways. However, the student who is looking for a framework of precise information may at times find himself confronted with the difficult task of separating well-documented facts from impressions, the imperative from the less significant. From this viewpoint, the reviewers feel the book could be improved.

J. O. C. E. and G. B. S.

(Continued on page A-148)

5-year study[1] with COUMADIN demonstrates: long-term anticoagulation in office management of outpatients is practical and effective

A 5-year study[1] of long-term anticoagulation with COUMADIN (warfarin sodium) in office practice patients has demonstrated that such treatment reduces the probability of further infarctions in the postinfarct patient and is effective in preventing a first infarction in patients with angina.

An earlier report[2] noted that long-term anticoagulant therapy with warfarin sodium can be carried out, along with the necessary prothrombin time determinations, as part of general office practice.

"The most significant advantage is the great ease in maintaining patients in a therapeutic range. It has been rewarding to find, month after month, patients varying no more than three or four seconds in their prothrombin times on their established dosage of Warfarin sodium [COUMADIN]."[1]

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the original and only warfarin responsible for establishing this drug as closely approaching the ideal anticoagulant[3,4] and as "the best anticoagulant available today."[5] Over 179,000,000 doses administered to date.

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Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. Maintenance, 5-10 mg. daily, or as indicated by prothrombin time determinations.

1. Nora, J. J.: M. Times, May, 1961. 2. Nora, J. J.: J.A.M.A. 174:118, Sept. 10, 1960. 3. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958. 4. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13. 5. Meyer, O. O.: Postgrad. Med. 24:110, Aug., 1958.

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► THE MANAGEMENT OF PEDIATRIC PRACTICE

By Hugh C. Thompson, M.D. and Joseph B. Seagle, M.D., Department of Pediatrics, Tucson Clinic, Tucson, Arizona. 172 pages, illustrated. 1961, Charles C Thomas, Springfield, Illinois. $7.50.

The authors of this book have set down the fruits of their experience in a combined pediatric practice covering 35 years in three different sections of the United States. Their premise is that a successful pediatric practice should provide an adequate number of satisfied, loyal and interesting patients so that working hours are challenging and full and both income and leisure time prove satisfactory.

Residency training teaches high-quality pediatric care, but it fails to furnish the essentials of practice management. The authors have ably corrected this deficiency in their readable book. The text is divided into two parts. The first, entitled "The patient comes first," discusses the pediatrician's relation to various members of the patient's family, the art and technics of practice, the office layout, waiting, and financial matters. The second section, "For the doctor," deals with utilization of employees, the telephone problem, professional expenses, relations with professional personnel, molding the practice to fit the individual doctor's needs, paper work, and life outside the office.

In answer to recent articles critical of pediatric practice, the authors state that pediatrics offers a challenging and rewarding career which requires understanding of and compassion for people and their problems. Much is routine, but an interest in the personalities involved and a sense of humor help to prevent monotony. The strong tendency of children to recover is a great aid in serious illnesses, and most pediatric patients mature to the full flower of adult life, which is gratifying to the pediatrician. Although pediatrics is not the most lucrative specialty nor the one with the shortest hours, the physician who practices it well will be richly rewarded by respect and affection from the families for whom he cares.

S. D. M.

Books received are acknowledged, and, as space permits, those of principal interest to our readers are reviewed more extensively. Listings of books received are on page 627.

RICHARD ARMOUR

PREDICTION

Doctors admit they cannot predict with accuracy the age when an infant will start sleeping through the night.—*News item.*

This will come as quite a shock
To those who count on Dr. Spock,
Will undermine the faith, as well,
Of those who swear by Doc Gesell.

Yes, even men with lofty domes
Who write authoritative tomes
Can't tell the parent (haggard, glum)
Just when the happy change will come.

But come it will, though not on charts,
When red are eyes and leaden hearts,
And once despairing Dad and Mother
Will start to think, "Let's have another."

NOTE TO PSYCHIATRISTS

Dr. Bernard I. Kahn, chief of psychiatry at the Kaiser Foundation in San Francisco, believes dancing is a definite aid in mental health.—*News item.*

Here is a thought that's quite entrancing:
Just send your nervous patients dancing.
Prescribe, instead of tranquilizers,
For those who tensely grind incisors,
A course, mayhap, with Arthur Murray,
And tell them they had better hurry.

Yes, pluck them from that darkened hall room
And recommend a nearby ballroom
Where lights are low and music jolly
And partners beautiful. By golly,
Let nervous cutups cut a rug
And those with jitters, jitterbug!

6
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N
T
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products to remember!
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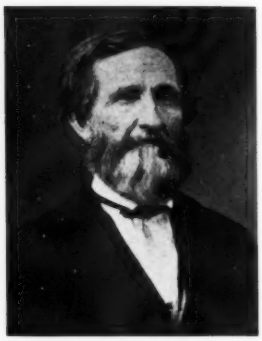
Great Names in American Medical History



Georgia

Crawford Williamson Long, M.D.

This is one of a series of biographical sketches of outstanding physicians of the past from each of the 50 states. Selection of subjects has been made by the medical society of each state or its designated committee.

CRAWFORD Williamson Long was born in Danielsville, Georgia, on November 1, 1815. At age 14 he entered Franklin College, now the University of Georgia, and at age 19 graduated with the degree of Master of Arts. He taught for one year in the Danielsville Academy, and then began the study of medicine under Dr. Grant of Jefferson, Georgia. After one year of this type of study he took a medical course at Transylvania College in Kentucky. Then in 1837 he entered the medical school of the University of Pennsylvania, and received his M.D. degree in 1839. Thereafter he was an intern in New York City, where he spent 18 months "walking the hospitals," working with such great teachers as Valentine Mott and Willard Parker. At 26 years of age, he returned to Georgia and bought the office of his old preceptor, Dr. Grant.

Well-confirmed rumor says that the young people of Jefferson occasionally had parties at which they inhaled laughing gas just for the fun of it. Dr. Long had participated in "ether parties" in Philadelphia, and he sent away to get some ether for similar parties in Georgia. He observed that some of the young men, while under the influence of ether, fell and incurred bruises without experiencing any pain.

In 1842 Dr. Long operated on a man named James Venable and removed two cysts from his neck, giving him some ether to inhale so that the operation was painless. Not until 1847 did William Thomas Green Morton of Massachusetts publish his results of work done with ether anesthesia in 1846. Dr. Long failed to publish his work, and it remained for later historians to give him credit as one of the first to use ether anesthesia.

Dr. Long died June 16, 1878. On September 15, 1957, the Long Memorial Museum was dedicated at Jefferson, Georgia.

DR. Pepys' Pages

Personal Diary
and Observations on
Medical Life
by MORRIS FISHBEIN, M.D.

Apr. 1—Late came Dr. Tarik Kapicioglu of Istanbul and Nurse Oskay, whom we met on our first visit to Turkey. She is now working in Augustana Hospital and he is here on a fellowship dealing with isotopes.

Apr. 2—To luncheon with Justin and Ann and all the little ones, who had a most successful morning pursuing hen fruit about the home. In the afternoon to visit Marjorie and Lester and all their little ones, and then late in the afternoon with Peter Friedell driving homeward well content.

Apr. 3—At noon to luncheon with Lou Zahn, Harry Becker and Judge Braude and Mrs. Margolis of New York to consider promotional efforts for the Weizmann Institute.

Apr. 4—To the Chicago Heart Association, and in the evening came Justin and Ann to dine with their brood, who have spent the week end with us.

Apr. 5—Early to the office of Dr. Samuel Meyer, and he found but slight change in my optic ability. At noon to the Covenant Club with Kauffman, Dachman, Drapman, Holland and others, and designing the program for the next "Salute to Medical Research." In the afternoon came Prout and Bruce from Mead Johnson in Evansville to display a new program of announcements to encourage good will for the medical profession, and thought them excellent indeed.

Apr. 6—By jet to Miami, and to the Diplomat Hotel for meetings of the National Foundation. This afternoon came Messrs. Mann and Nederlander from Detroit and also Tracy Hare; so discussed with them a new medical project.

Apr. 7—Early awake and to play at golf with Mistress Pepys. In the afternoon to a meeting with some 20 physicians of Miami, including Litt, Shepperd, Russin, whom I knew well in Cincinnati, and many more, and there was much conversation about new approaches for organized medical service.

Apr. 8—This morning meeting Topping, Basil O'Connor, Bob Buerki and many others of the National Foundation. In the afternoon once more on the golf links, and in the evening dining with friends in the beautiful Ambassadors' Room of the Diplomat Hotel.

Apr. 9—Again conferences on various affairs and again golf and a blazing sun, and found that by this time the heat had produced various degrees of burning which were not the most comfortable and for which people with intelligence plan prevention rather than treatment.

Apr. 10—To the meeting of the Committee on Viruses and heard fascinating discussions of new research, in which the principal participants were Topping, Turner and Tatum. In the evening to the country club for a fine reception and dinner for all the members of the various commissions and of the staff. Here old Pepys and his lady sat with the Dwight Ingles and the Boyds for abstruse conversation and excellent anecdotes.

Apr. 11—A great group assembled to hear of advances in knowledge of birth defects and in the study of rheumatoid arthritis, and the necessity for breaking new ground is just as apparent now with these subjects as with the viruses 50 years ago.

Apr. 12—This morning the congress considers problems related to education and training and the marvelous results achieved by the fellowships granted in many projects over the last 25 years. Particularly new are the great numbers of sociologic studies. Lester Evans tells that there is now a special society of sociologists who are concerned with problems of medical care and administration.

In the evening came my sister Jennie Rauh and my niece Brenda, and all dining and then to visit Jean King and Harry with their new establishment for leather goods and other novelties, and Mistress Pepys enjoyed what is commonly called a "shopping field day."

Apr. 13—Now come the problems relating to the care of those with whom the Foundation is concerned, with Walter Bauer presiding and William Clark pitching, and here were most interesting discussions of changes in the care of the sick. So at lunch with Norm and Helen Topping, and then by jet back to Chicago.

Apr. 14—To appear on Don McNeill's program and for some 25 minutes answering questions. In the evening to attend the great ball honoring 35 years of service of Dr. M. Edward Davis to the Chicago Lying-in Hospital, and renewed again my friendship with Lawrence Kimpton, Kirkpatrick, Coggeshall, LeRoy, Bennett, and many of the greats from the University.

Apr. 15—Early came a call that Grandma Mantel, now nearing 93, has fractured a hip. And so the rest of the day in the hospital, where the fracture was suitably nailed by Dr. Barnett and the response to her care immediate and good.

Apr. 16—All this day the city lies beneath the snow and old Pepys spends most of the day at the hospital, and in the evening dined with the family.

Apr. 17—Much of the time spent observing the gradual recovery of Grandma Mantel.

Apr. 18—At noon came Drs. Lowell Coggeshall and Albert Dorfman to consider the future of research at La Rabida, for rheumatic fever continues to decline in both incidence and morbidity. In the evening to speak for the South Shore Branch of the National Council of Jewish Women at the Y.M.C.A., and found some 50 ladies who were happy to be engaged in good work.

Apr. 19—Early to the office of Albert Pick and there with DeMets, Frieder and Snook to work out the nominations for the annual meeting of La Rabida. At noon to the Chicago Heart Association, sitting with Victor Cullen, chairman of the board, Louis deBoer, our executive, and the staff members who work out plans for our annual meeting. Late in the afternoon to Lincoln, Nebraska, where to the airport came Dr. Fuenning, and with

(Continued on page A-162)

inside as well as outside the hospital... staphylococci usually remain sensitive to

CHLOROMYCETIN

(chloramphenicol, Parke-Davis)

That the sensitivity patterns of "street" staphylococci differ widely from those of "hospital" staphylococci is a well-established clinical fact.[1-5] Although strains of staphylococci encountered in general practice have remained relatively sensitive to a number of antibiotics,[6] the problem of antibiotic-resistant staphylococci appears to be a threat to all patients in hospitals today. It is encouraging to note, however, "...that a relatively small percentage of strains develop resistance to chloramphenicol, despite the consumption of large amounts of this antibiotic."[7]

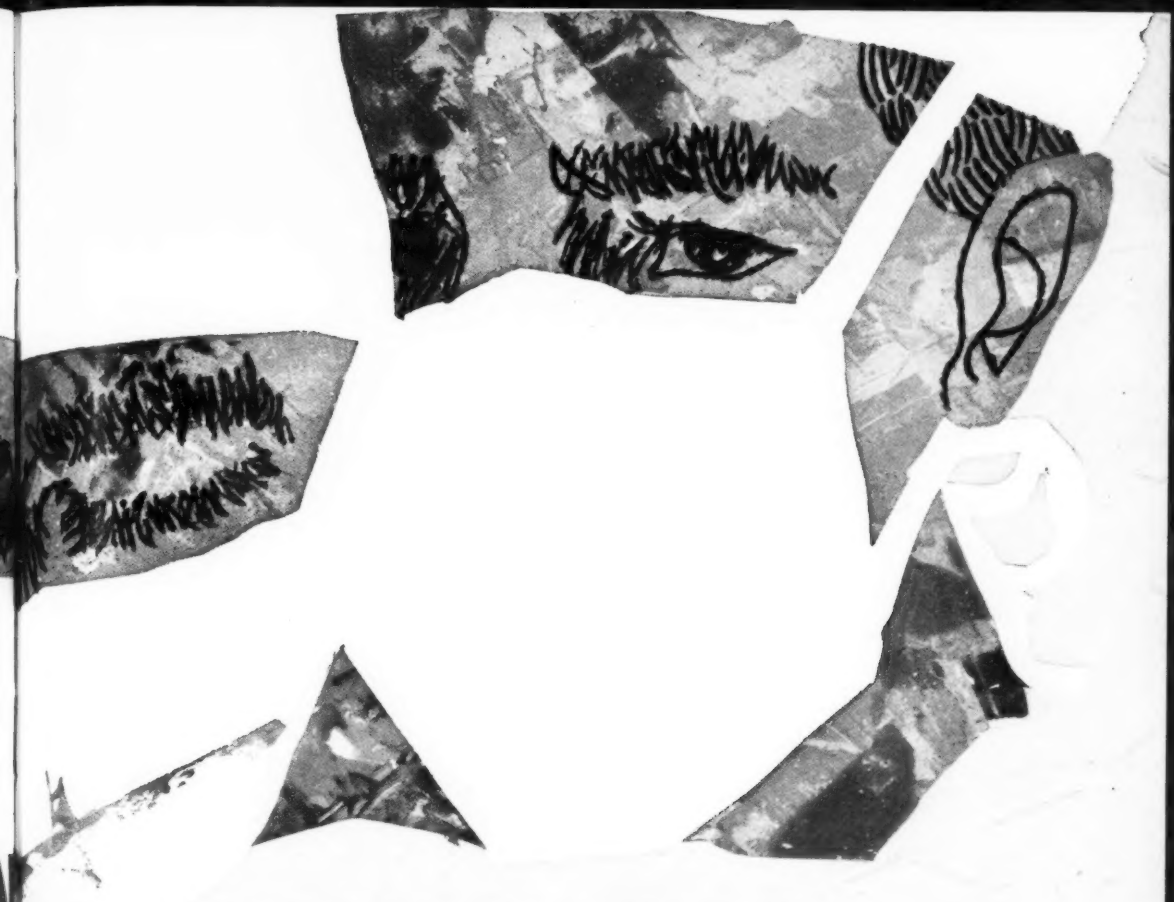
In one hospital, for example, CHLOROMYCETIN "...was the only widely used antibiotic to which few of the strains were resistant."[8] In another hospital, despite steadily increasing use of CHLOROMYCETIN since 1956, "...the percentage of chloramphenicol-resistant strains has actually been lower in subsequent years."[9] Elsewhere, insofar as hospital staphylococci are concerned, it appears that "...the problem of antibiotic resistance can be regarded as minimal for chloramphenicol."[10]

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

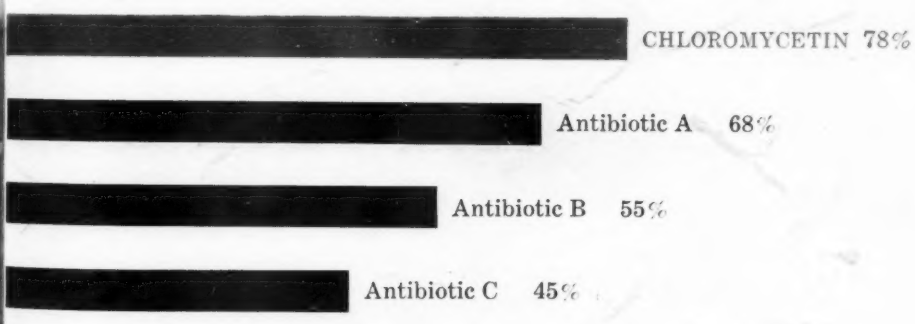
See package insert for details of administration and dosage.

Warning: Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after short-term and with prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.



IN VITRO SENSITIVITY OF 250 STRAINS OF STAPHYLOCOCCI TO CHLOROMYCETIN AND TO FOUR OTHER ANTIBIOTICS*



These strains of coagulase-positive staphylococci were isolated from hospitalized patients at a large county hospital during the year 1959. Sensitivity tests were done by the disc method.

*Adapted from Bauer, Perry, & Kirby[1]

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PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

him to the Cornhusker Hotel, being greeted again by my host of some years past.

Apr. 20—Early to the radio station in Lincoln, and then to speak to the university high school teen-agers about problems of marriage and similar relationships. Next to talk on modern marriage and family living to members of the faculty. At noon to luncheon with the deans of seven of the colleges and thereafter addressed the students in the graduate school. Next to visit the university museums, which are miniatures of the Museums of Natural History and of Science and Industry in Chicago. To dine with the "DAMES," who are the young marrieds of the university, and to speak in a public forum on modern problems of marriage counseling. After that to talk for an hour with Dr. Fuenning, chief of health services at the University of Nebraska, before the Burlington left for Chicago.

Apr. 21—Early came Miss Karlsteen and Mrs. Woods of Polk Bros. to discuss making a tape recording under the title "Keep Your Husband Alive." In the afternoon to greet Albert Pick for the dedication of the Pick-Congress Hotel's new Great Hall, which is a beautiful auditorium, and found there also Maurice Goldblatt, Judge Burke and other members of the board of the Cancer Foundation, and we held a quick board meeting. In the evening reading the new work of John Dos Passos called "Midcentury," in which he weaves into a novel the high lights of the 1950s in America, with interesting brief biographies of the great labor leaders.

Apr. 22—Finally getting the surface of the desk visible; in the evening playing at "Scrabble" and at the same time observing television. Read Mykle's "Lasso Round the Moon," which is Norwegian realism.

Apr. 24—With Mrs. Margolis discussing promotion of the Weizmann Institute, and then with Floyd Landis to plan a great banquet to dedicate the University of Chicago's Diagnostic Center. In the evening with Dr. Niels Dungal of Reykjavik, Iceland, Paul Szanto, pathologist at the Cook County Hospital, and the Friedells to dine at the new Cafe Bonaparte of the Blackstone, and heard Hildegarde chirping away as she has done for these many years. Thereafter all to visit her in her apartment, where she had much to say about her newest venture into vitamins and amino acids. But this is not the cause of her youthfulness; it is her inner spirit, which is the spirit of youth.

PROOF-POSITIVE

The psychiatrist, exhausted by his difficult patient, asked, "Are there any other instances of mental disturbance in your family?"

"There must be," said the patient, "they keep sending me letters asking for money."

* * *

JUST A CASE

They told him he was cured and could pack and leave the sanatorium.

"What do you plan to do?" asked the administrator.

"I haven't made up my mind," was the answer. "I may resume practice. Then again I thought of journalism. However, most probably I'll be a coffeepot."

* * *

HE GREW UP

"When I was seven years old," said the juvenile delinquent, "I asked my parents where I came from. When I was 15 I told them where to go."

* * *

Apr. 25—At noon to meet with the committee for the City of Hope and worked out further plans for the "Salute to Medical Research." Thereafter to station WAIT for an interview by Phil Lind on the book "Heart Care." Next to the stage of our great Civic Opera, where in the setting of the second act of "Carmen" was held the annual meeting, with a complete Spanish dinner which an audience of some 400 enjoyed.

The new directors were elected, and, in the midst of all this, the presiding of Nicholas Galitzine was as charming as Victor Borge at his best. The French consul not only praised the culture of Chicago, but also told the latest word on the success of De Gaulle over the revolting generals.

Apr. 26—At noon to the University Club, where the Hyde Park Bank gave a reception for our new chancellor Beadle. Louis Mann made the introductions, and old Pepys sat with Arthur Rubloff, Schoenstadt and Coggeshall, and we discussed many matters of civic and scientific importance.

Apr. 27—In Detroit attending morning sessions of the American College Health Association, dealing with problems of physical examination. At 11 A.M. came Dan Price to make six tape recordings on the subjects of medical care for the aged, the attack on quackery, the importance of counseling, and similar subjects. At noon with Jack Mann and his son and Nederlander to Mario's and found the food superb. Thereafter to speak for an hour on counseling in the great McGregor Hall of Wayne State University, and then came a panel of psychiatrists to discuss further the questions of counseling. Then by jet to Chicago in 31 minutes.

Apr. 28—To lunch with Floyd Landis and Maurice Goldblatt to work out final plans for the University of Chicago dinner on June 1, which should be a great occasion. Reading now the life of Toulouse-Lautrec and at the same time a novel of ancient Israel called "Rizpah," by Charles E. Israel, and find both works fascinating as one passes easily from one to the other. At night to the home of Carol Gibbs and there met Rand of New York, and had an inviting dinner.

Apr. 29—In the morning came the Drs. DeYoung to inquire about medical writing and its technics. In the afternoon observing the Cubs in baseball with the Dodgers, and reading also a treatise on venereal disease written by N. D. Falck in 1774, and some of his observations were so erudite as to be amusing. In the evening to dine came brother Albert, and thereafter old Pepys surrendered in mathematics, although the occasion was hardly long enough to demonstrate skill.

Apr. 30—Until early afternoon at the desk reading many works just off the press and then to hear the famous Netherlands orchestra, and the audience came forth with a tremendous ovation. Next, to a reception given by Consul General Hooft Graafland and his lady, and met here many of our friends among the consulates and the leading Dutch citizens of Chicago. Thereafter to the restaurant of my friend Henry Moy, now called Hoe Kow, and partook of the finest Chinese food, and greeted again Mrs. Moy and many others who find this cuisine delightful.

1 Assembly—Interstate Postgraduate Medical Association—Cleveland—November 13-16

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Postgraduate Medicine

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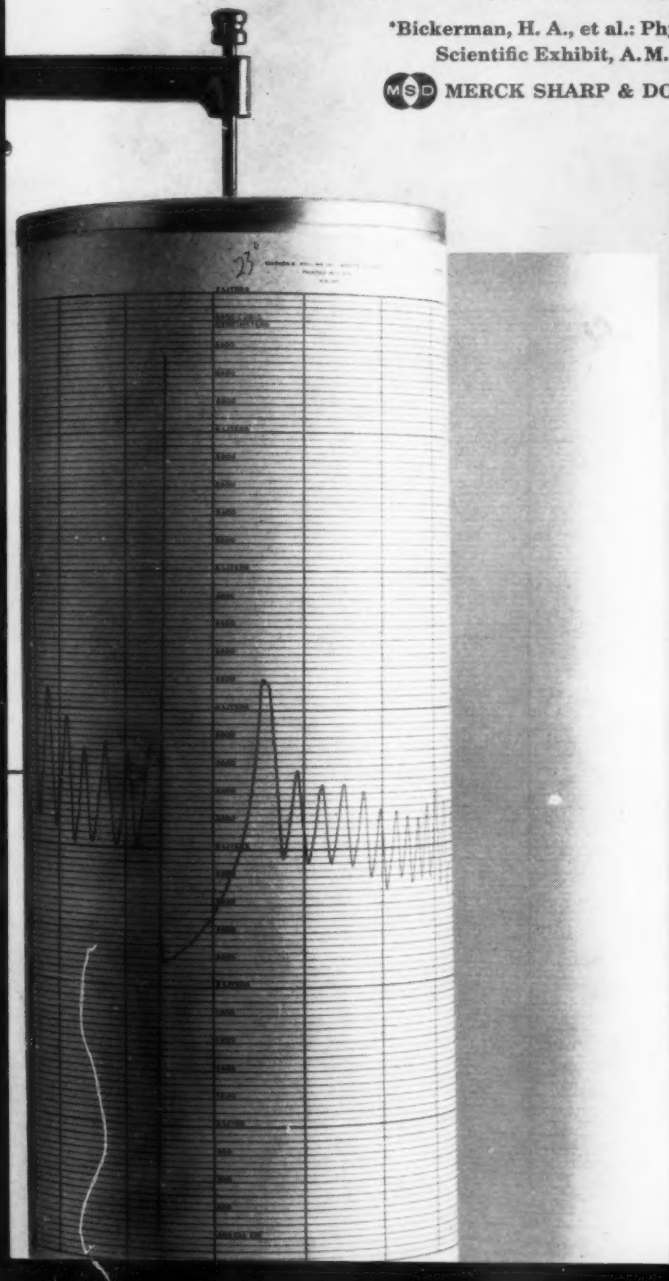

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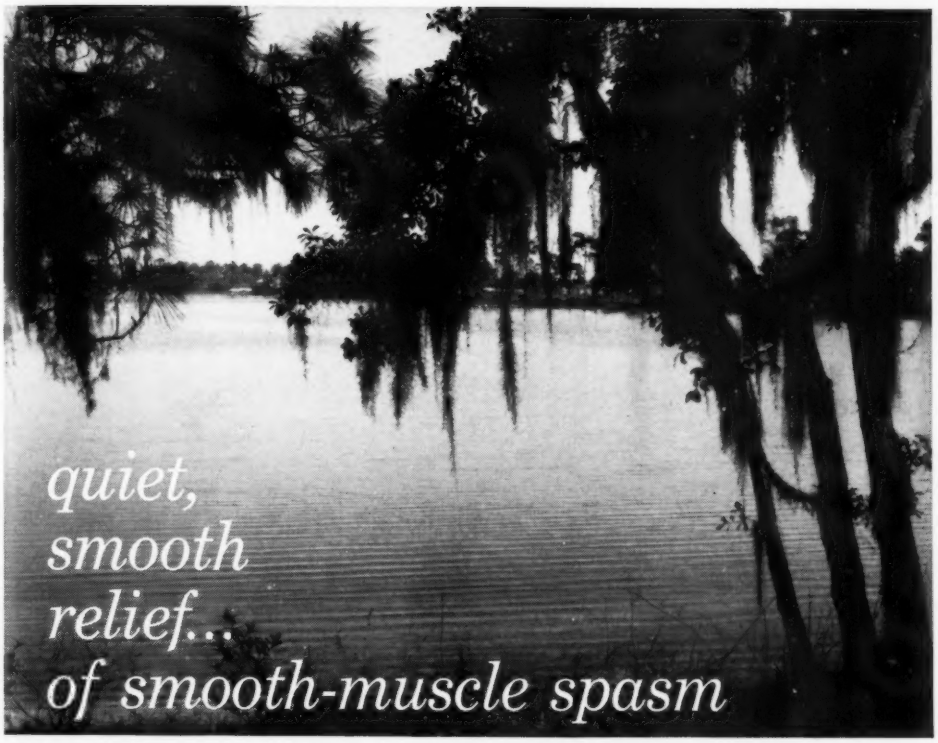

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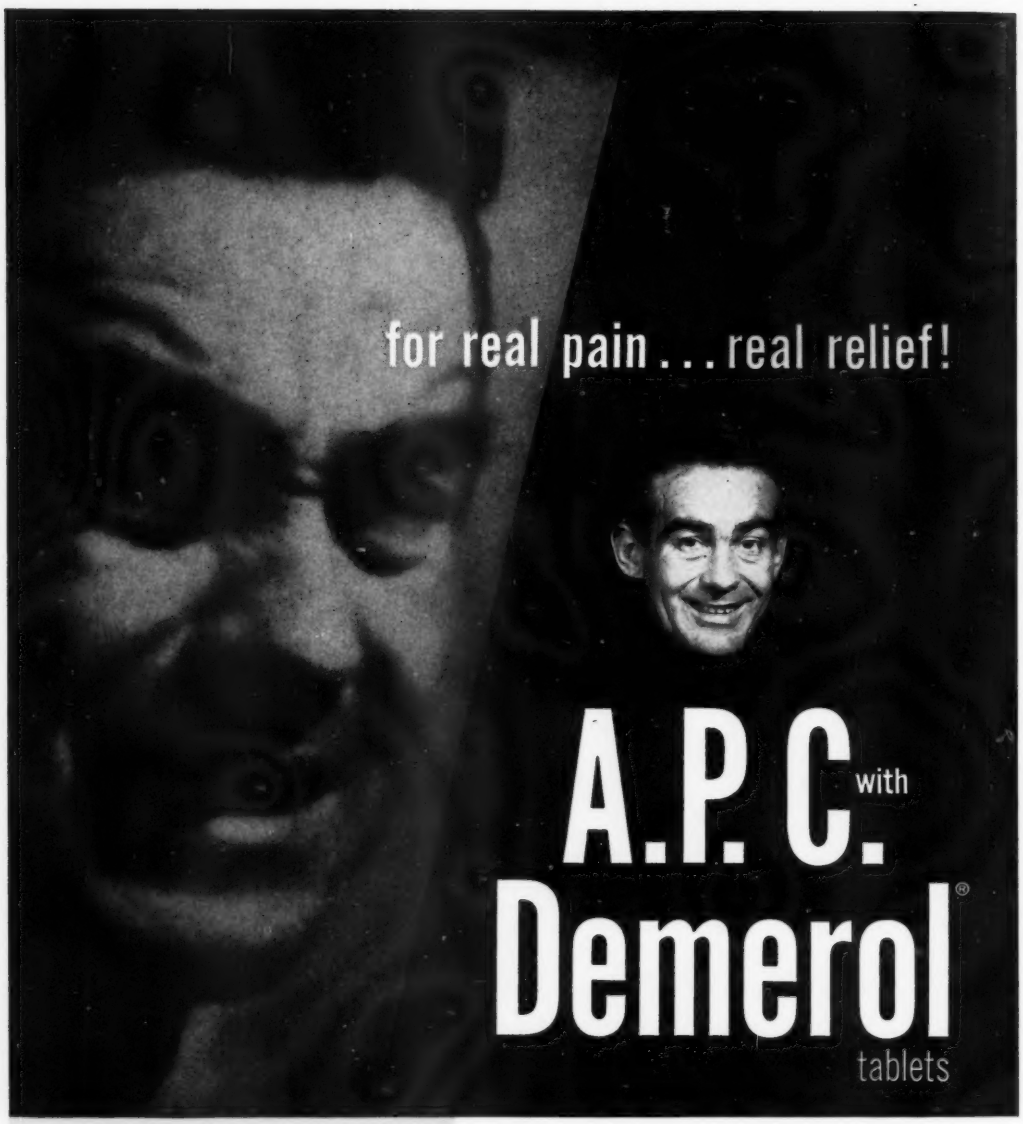

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Case data courtesy Henry Dolger, M.D.

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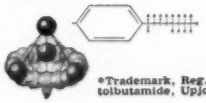

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*Doshay, L. J., and Constable, K.: Treatment of Paralysis Agitans with Chlorphenoxamine Hydrochloride, J.A.M.A. *170*:37 (May 2) 1959.

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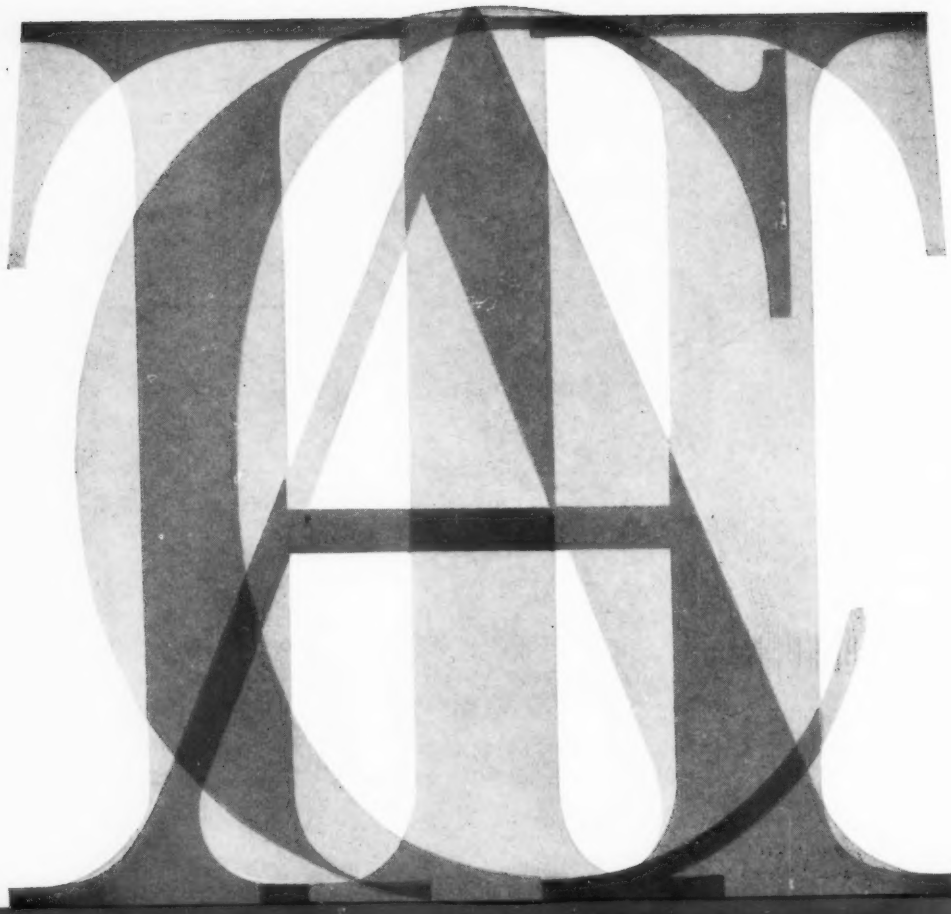

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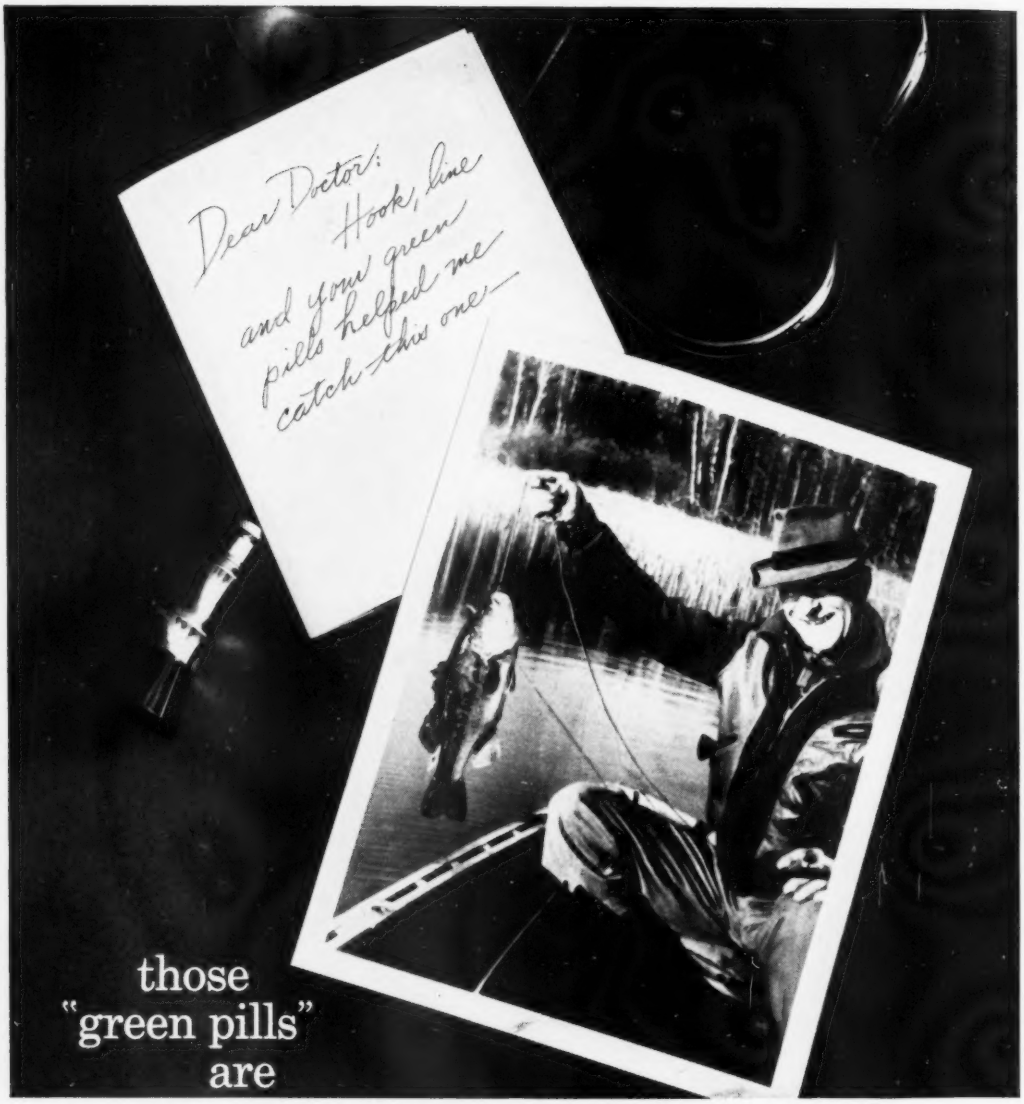

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Before and after vaginal surgery in postmenopausal patients		
Vulvovaginitis (as an adjunct to anti-infective or other supportive measures)	Pruritus, burning; inflammatory tissue reaction.	**"Premarin"® H-C Vaginal Cream** 0.625 mg. conjugated estrogens, equine and 1.0 mg. hydrocortisone (present as acetate)/Gm., in a nonliquefying base. (Also contains citric acid, sodium citrate, glycerin, spermaceti, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenyl mercuric acetate, sodium lauryl sulfate, liquid petrolatum and D&C orange No. 3.)
Monilial Vaginitis (also as an adjunct in trichomoniasis, alone or accompanied by moniliasis)	Mild to severe pruritus is predominant symptom; little or no leukorrhea. **NOTE:** Monilial vaginitis is frequently associated with diabetes mellitus.	**"Vanay"® Vaginal Cream** 250 mg. Triacetin/Gm., in a nonliquefying base. (Also contains polyoxyethylene sorbitan monostearate, glyceryl monostearate, silicon dioxide and titanium dioxide.)

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Provides tissue-building action of topical estrogen to help counteract senile tissue atrophy. Prompt healing and enhanced resistance to infection follow improvement in texture and vascularity of vaginal mucosa.	Average dosage: 2 to 4 Gm. daily depending on severity of infection. **NOTE:** Use in atrophic lesions of the vulva does not preclude necessity for careful diagnostic measures to eliminate possibility of neoplasia.	Combination package: No. 874 — Each contains 1½ oz. tube with 15 disposable applicators. (Direction sheet for use also enclosed.)
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Anti-inflammatory and antipruritic effects of hydrocortisone provide prompt relief of initial distress; topical estrogen exerts specific action to elicit physiologic tissue response.	Average dosage: 2 to 4 Gm. daily. Continue for at least 7 to 10 days after symptoms subside.	Combination package: No. 216 —Each contains 1 oz. tube with 15 disposable applicators. (Direction sheet for use also enclosed.)
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*Junkmann, C.: Unpublished reports cited by Werner-Boschann, H.: *Ann. New York Acad. Sc.* 71:727-752, 1958.

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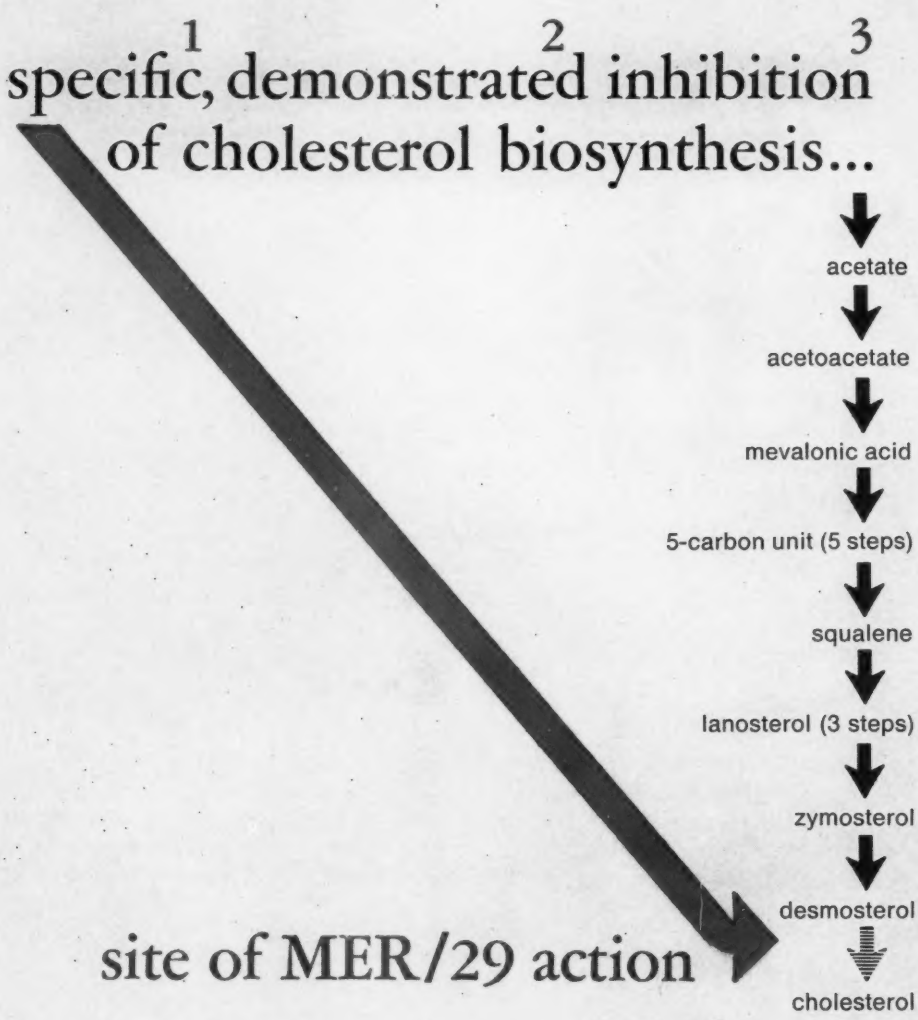

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—National Heart Institute: Diet, Hormones, and Atherosclerosis..., Bethesda, Md., U.S. National Institutes of Health, 1958.

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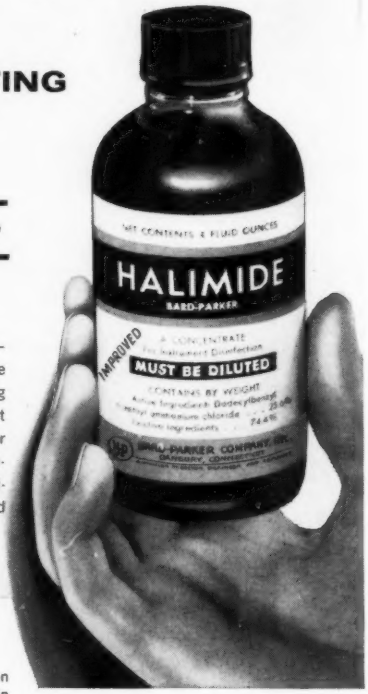

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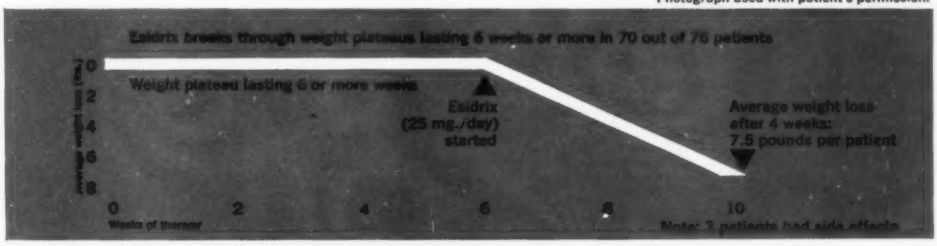
Esidrix breaks through weight plateaus lasting 6 weeks or more in 70 out of 76 patients
Weight plateau lasting 6 or more weeks
Esidrix (25 mg./day) started
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Weeks of therapy
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(Adapted from Einhorn and Kalb[2])

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References: 1. Ray, R. E.: To be published. 2. Einhorn, H. P., and Kalb, S. W.: Clin. Med. 7:1995 (Oct.) 1960.

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In Brief Niamid, brand of nialamide, is 1-(2-[benzylcarbamyl] ethyl)-2-isonicotinyl-hydrazine, a well-tolerated antidepressant that may correct or relieve depression on once-a-day dosage. **Indications:** Depressive syndromes of varying degrees of severity may be responsive to Niamid including: involutional melancholia, postpartum depression, depressed phase of manic-depressive reaction, senile depression, reactive depression, schizophrenic reaction with depressive component, psychoneurotic depression. ■ In neurotic or psychotic patients, Niamid may normalize or favorably modify aberrant or excessive reactions and symptoms of depression such as: phobias, guilt feelings, dejection, feeling of inadequacy, discouragement, worry, uneasiness, distrustfulness, hypochondriacal and nihilistic ideas, difficulty in concentration, insomnia, loss of energy or drive, indecision, hopelessness, helplessness, decreased functional activity, emotional and physical fatigue, irritableness, inability to rest or relax, sadness, anorexia and weight loss, and withdrawal from society. *In the withdrawn patient,* Niamid may elevate the mood so that there is increased activity, increased awareness and interest in surroundings, and increased participation in group activities. Appetite may be increased and there may be decreased fatigability. Lack of clinical response to other antidepressant therapy does not preclude a favorable response to Niamid. Relief of depression may also be evidenced by elimination or reduction of the need for somatic therapy, such as electroshock. *In patients suffering from depression associated with chronic illness,* Niamid may improve mental outlook, reduce the impact of pain, decrease the amounts of narcotics or analgesics needed, and improve appetite and well-being. *In patients with angina pectoris,* Niamid has been found to be a useful adjunct to management through reduction in frequency of attacks and pain. **Dosage:** Starting dosage is 75 to 100 mg. on a once-a-day or divided daily basis. This may subsequently be adjusted depending upon the tolerance and response. Responses to Niamid are not usually rapid, and revisions of dose should be withheld until at least a few days have elapsed at each level. Increments or decrements of 12½-25 mg. are generally sufficient. A daily dosage of 200 mg. is the maximum recommended for routine use. (As much as 450 mg. daily has been used in some patients.) **Side Effects:** Niamid, in clinical use, has been characterized by a significant lack of toxicity. It is generally well tolerated. Nervousness, restlessness, insomnia, hypomania, or mania, sometimes occur. Occasional headache, weakness, lethargy, vertigo, dryness of the mouth, blurred vision, increased perspiration, constipation, mild skin rash, mild leukopenia, and epigastric distress may be obviated or modified by reductions in dose. Effects due to monoamine oxidase inhibition persist for a substantial period following discontinuation of the drug. **Precautions and Contraindications:** Hepatic toxicity has not been reported in extensive clinical studies. 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Rare instances have been reported of reactions (including atropine-like effects, and muscular rigidity) occurring when imipramine was administered during or shortly after treatment with certain other drugs that inhibit monoamine oxidase. **In Cardiology:** The central effects of Niamid may encourage hyperactivity and the patient should be closely observed for any such manifestation. Orthostatic hypotension or hypertensive episodes occur in a few individuals; cardiac patients should be carefully selected and closely supervised. **In Epilepsy:** Although in some patients therapeutic benefits have been achieved with Niamid, in others the disease has been aggravated. 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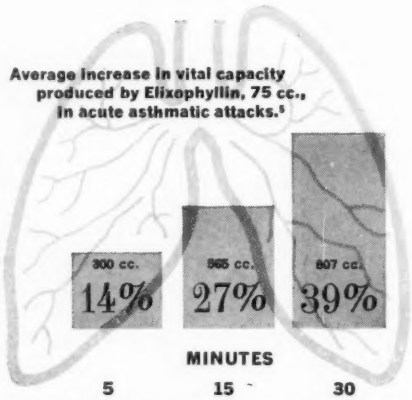

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*Pomeranze, J.: J. New York M. Coll. *1*:32, 1959.

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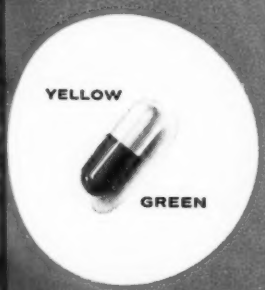

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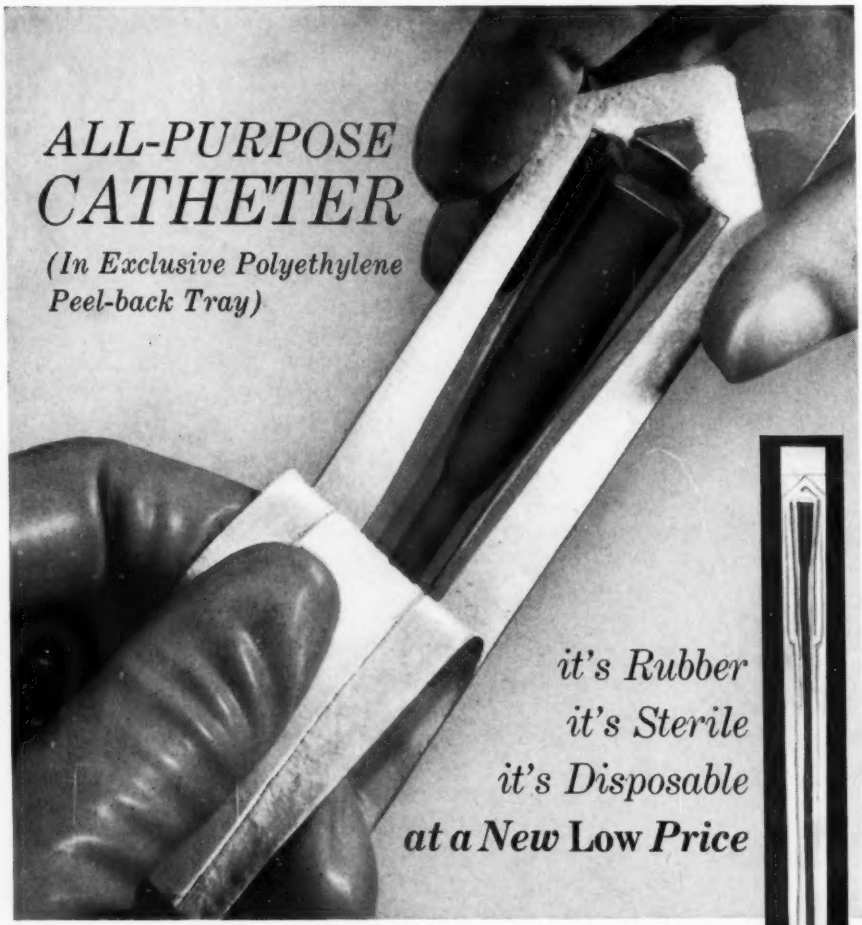

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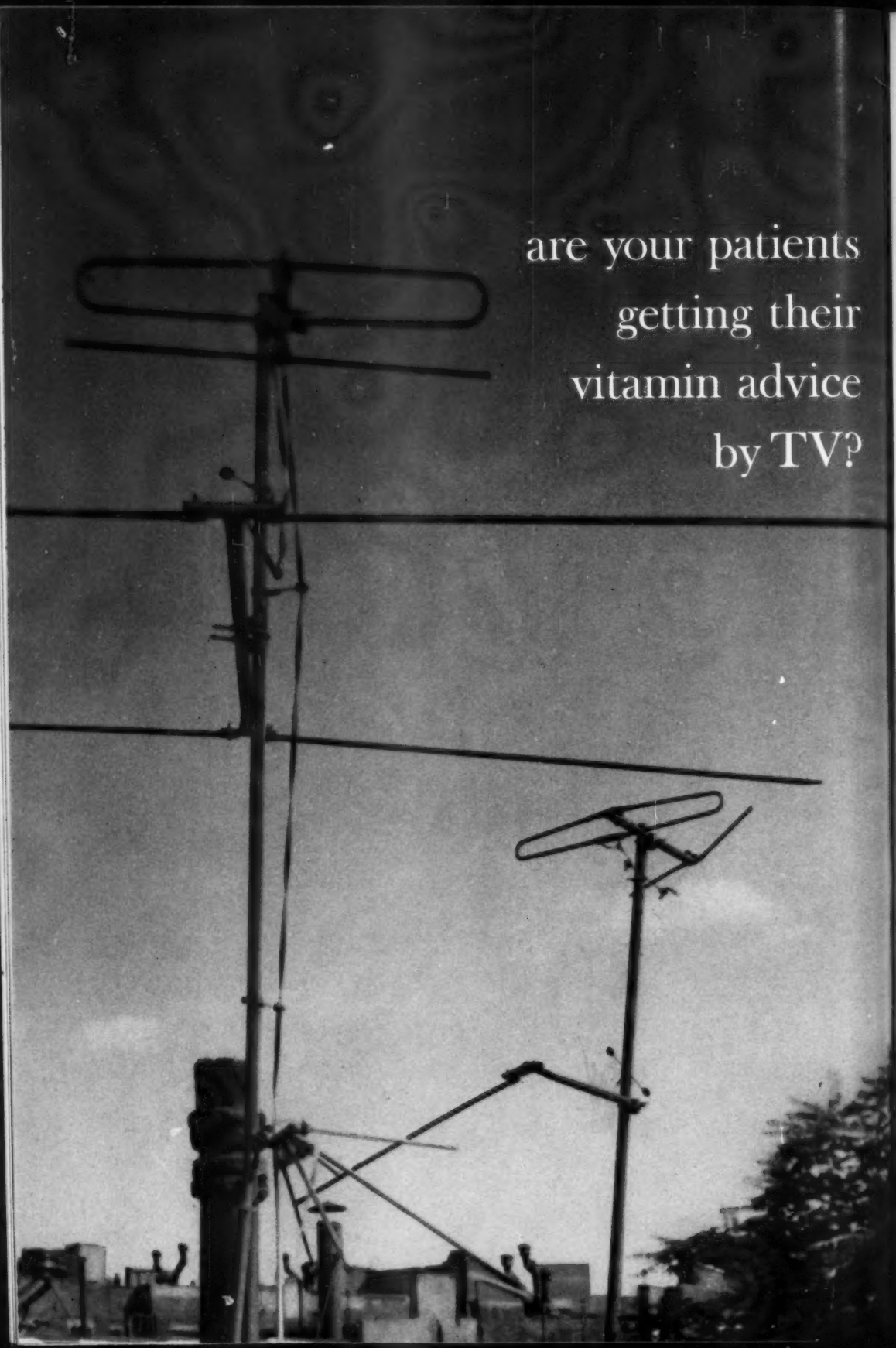
One of the most important problems facing the medical profession today:

Your specification versus TV advice ▶


are your patients
getting their
vitamin advice
by TV?

don't let medical control out of your hands during the critical newborn period

The rising tide of commercialism in health—by television, mail order, door-to-door salesmen—is taking medical control out of your hands during the critical newborn period. Only *you* can counter the dangers of non-professional medical advice. Mothers look to you for guidance in every step of baby's growth and development—the responsibility for the newborn's medical care is yours—yours alone.

An important way to establish your medical control early is through specification of an established ethical vitamin preparation. When prescribing for the newborn, consider the outstanding advantages of new, improved Vi-Sol® vitamins. Carefully reformulated after consideration of the recommendation of authorities,* Vi-Sol vitamins provide rational, practical, safe levels of vitamins C, D and A.

Whenever drops are outgrown, comparable improvements in levels of C, D and A are also offered the older child in Vi-Sol chewable vitamins and Vi-Sol teaspoon vitamins.

*Recommended Daily Dietary Allowances established by the National Research Council, and endorsed by the Council on Foods and Nutrition of the American Medical Association, "Vitamin Preparations As Dietary Supplements and As Therapeutic Agents," J.A.M.A. *169*:41-45 (Jan. 3) 1959.

new VI-SOL® vitamins

TRI-VI-SOL®	POLY-VI-SOL®	DECA-VI-SOL®
Vitamin Drops	Vitamin Drops	Vitamin Drops
	Teaspoon Vitamins	Teaspoon Vitamins
Chewable Vitamins	Chewable Vitamins	Chewable Vitamins
Vitamin Drops with Iron		Chewable Vitamins with Iron

Mead Johnson Laboratories

Symbol of service in medicine

331861

Helps you take the misery out of menopause

as hormones alone often don't do

Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

Dosage: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

Composition: Miltown (meprobamate) + conjugated estrogens (equine).

Supplied: **Milprem-400**, each coated pink tablet contains 400 mg. Miltown and 0.4 mg. conjugated estrogens (equine). **Milprem-200**, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Both potencies in bottles of 60.

Literature and samples on request.

Milprem®

(Miltown® plus natural estrogens)

CMP-1306

Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

This is where Milprem helps you so much. It calms the woman's anxiety and tension; prevents moody ups and downs; relieves her insomnia and headache. At the same time, it checks hot flushes by replacing lost estrogens. The patient feels better than she did on estrogen therapy alone. And your counsel and your assurances can now help her make her adjustment much faster.

WALLACE LABORATORIES / *Cranbury, N. J.*

Carnalac meets the medical preference for the evaporated milk formula... in a convenient, ready-prepared form.

Carnalac is Carnation Evaporated Milk with its added Vitamin D, plus carbohydrate.

A properly proportioned formula is assured, even when Carnalac is prepared by the inexperienced young mother. She just adds water in the amount you recommend.

The proven nutritional value of evaporated milk formulas is assured with Carnalac. A history of many years of successful feeding with evaporated milk makes it the most widely used form of milk for infant feeding today.

Digestible, safe, uniform, stable. Carnalac is the same prescription quality as Carnation – the milk used in more hospital formula rooms throughout the world than all other brands combined.

Diluted 1:1, Carnalac provides 7.1% carbohydrate, 2.8% protein, 3.2% fat, 400 I.U. Vitamin D per reconstituted quart, 20 calories per fluid ounce.

WORLD'S LEADER BY FAR, FOR INFANT FORMULA FEEDING

"from Contented Cows"

CYCLEX®

HYDRODIURIL® WITH MEPROBAMATE
HYDROCHLOROTHIAZIDE

to relieve the symptoms of premenstrual tension

for EDEMA... CYCLEX provides the prompt diuresis of HYDRODIURIL for rapid reduction of weight gain, breast fullness, abdominal congestion

for MOOD-CHANGES... CYCLEX supplies the effective relief of meprobamate for nervousness, irritability, tension, nausea, malaise, insomnia

for GI DISTRESS... CYCLEX affords quick-acting relief of nausea and bloating associated with premenstrual tension

SUPPLIED: Tablets, bottles of 100. Each tablet contains 25 mg. of HYDRODIURIL (hydrochlorothiazide) and 200 mg. of meprobamate

DOSAGE: Usual adult dosage is one tablet once or twice a day, beginning on the first morning of symptoms and continuing until the onset of menses. CYCLEX may be continued through the menstrual period.

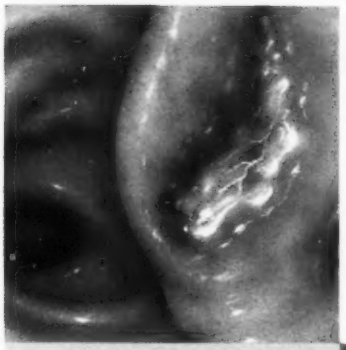
Before prescribing or administering CYCLEX, the physician should consult detailed information on use accompanying package or available on request.

CYCLEX and HYDRODIURIL are trademarks of Merck & Co., Inc.

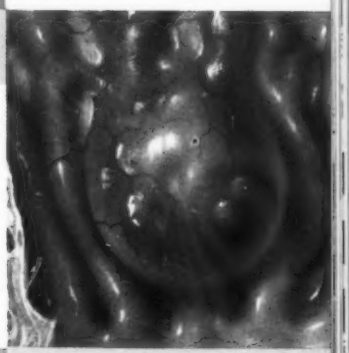
MSD

MERCK SHARP & DOHME
Division of Merck & Co., Inc.
West Point, Pa.

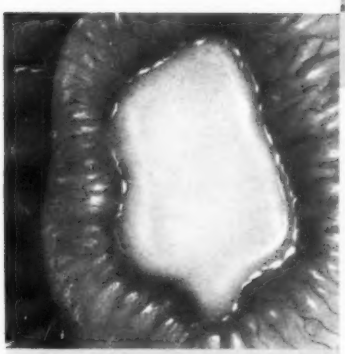
Effective topical steroid therapy in anorectal disorders relieves itching, burning and soreness, pain, pruritus. Tends to reduce inflammation and edema.



1. proctitis accompanying ulcerative colitis



2. acute internal hemorrhoids



3. radiation proctitis

Wyanoids® HC

Rectal Suppositories with Hydrocortisone, Wyeth

- for relief of pain and itching
- for promotion of tissue repair
- to avoid systemic steroid side-effects

clinical studies confirm safety and efficacy of topical hydrocortisone in anorectal disorders

anorectal inflammations: "Topical application of hydrocortisone suppositories (WYANOIDS HC) appears as effective as systemic corticoid medication for many proctologic inflammatory disorders and is complicated less frequently by undesirable side effects."

Marks, M.M.: Diseases of the Colon & Rectum *3*:250 May-June, 1960.

pruritus ani, proctitis, chronic ulcerative colitis, postoperative inflammatory reactions: "Topical hydrocortisone (WYANOIDS HC) proved to be free from corticosteroid side effects and its use was beneficial to 96 percent of the patients treated."

Schneider, H.C.: J. of the International College of Surgeons *33*:208 February, 1960.

radiation proctitis and idiopathic ulcerative colitis: "The advantages of topical steroid therapy are the rapidity of response, improvement not only symptomatic but by proctoscopic examination, minimal detectable degrees of absorption with avoidance of undesirable side effects of prolonged steroid therapy, and maximum concentration of the medication in the area of involvement."

Patterson, M., and McGivney, J.: South. M. J. *52*:423 April, 1959.

Wyanoids® HC

Rectal Suppositories with Hydrocortisone, Wyeth

---

to relieve anorectal itching, soreness, pain

Wyanoids®
Hemorrhoidal Suppositories, Wyeth

Wyanoid® OINTMENT
Hemorrhoidal Ointment, Wyeth

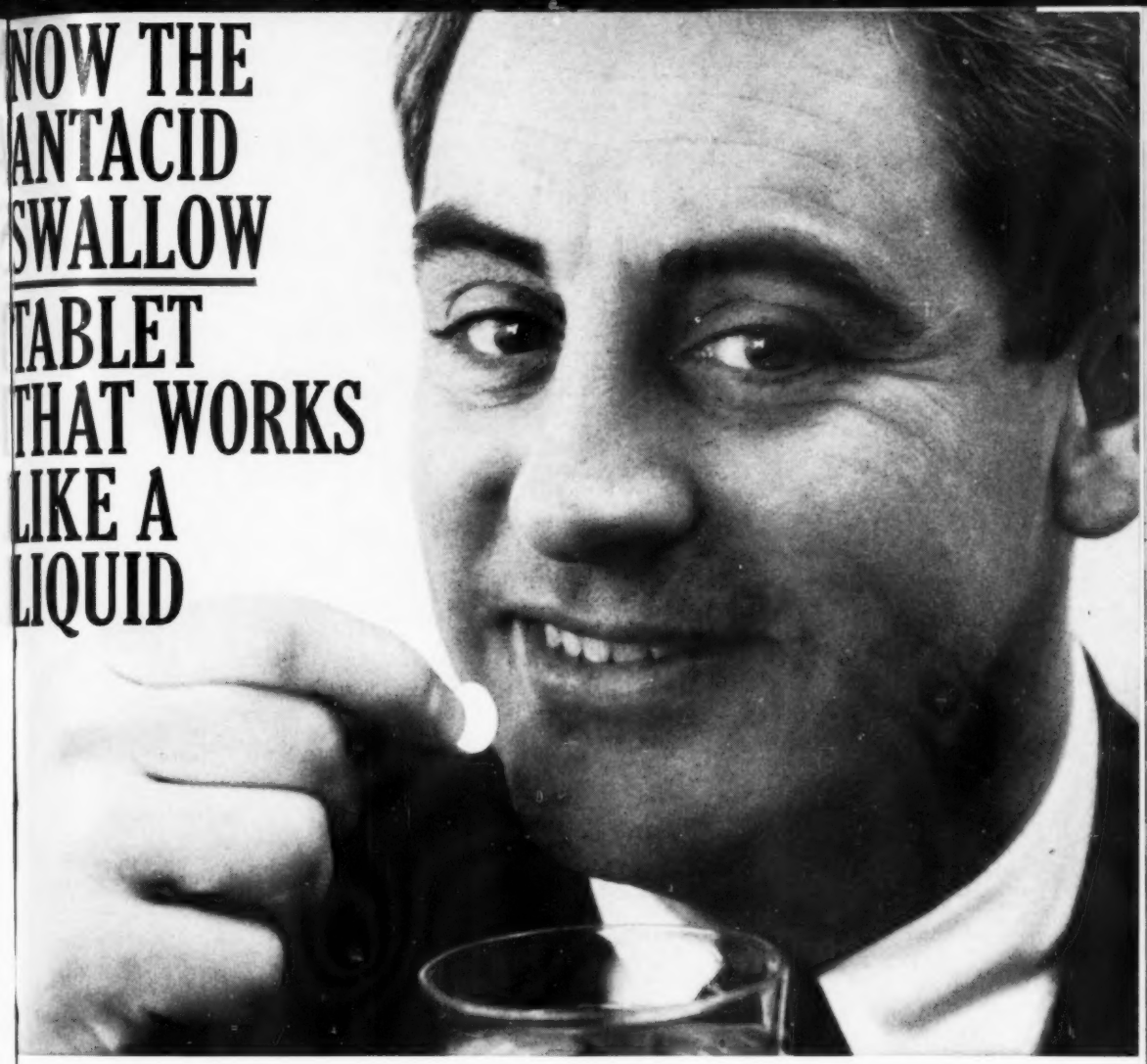
- **quick dissolving**
- **lubricates rectum**

Caution: Hydrocortisone should not be used until an adequate proctologic examination is completed and a diagnosis made. Other specific measures against infections, allergy and other causal factors must not be neglected. Preparations containing belladonna may produce blurring of vision, rapid pulse, or dryness of the throat. If these symptoms develop, use of the preparation should be discontinued.

Wyeth® SERVICE TO MEDICINE

Wyeth Laboratories Philadelphia 1, Pa.

NOW THE ANTACID SWALLOW TABLET THAT WORKS LIKE A LIQUID



A COMPLETELY NEW CHEMICAL ENTITY*

"RIOPAN"®

Brand of Monalium hydrate

A TRUE BUFFER-ANTACID
SWALLOW TABLETS & SUSPENSION

THE NON-CHEW TABLET THAT WORKS LIKE A LIQUID IN SPEED OF ACTION AND DURATION OF RELIEF

AYERST LABORATORIES
New York 16, N. Y. • Montreal, Canada

Ayerst®

- **works as <u>fast</u> as a liquid... adjusts pH to the safe 3.5-5.5 therapeutic range within seconds**
- **<u>sustains buffering action</u> like a liquid ... maintains a physiologic pH for prolonged periods**

LIQUID ACTION WITH TABLET CONVENIENCE

Now for the first time, your patients can enjoy **liquid effectiveness** with **tablet convenience** — and because "RIOPAN" is a **swallow** tablet, there is no taste fatigue...nor have side effects been a problem: no alkalinization—no acid rebound—no constipation—no diarrhea.

*THE PHARMACOLOGIC BASIS FOR "RIOPAN" EFFECTIVENESS

"RIOPAN" is an entirely new chemical entity in which two agents with well established antacid properties — magnesium and aluminum hydroxides—are united in a single molecule by a patented process (U. S. Pat. 2,923,660). This chemical union makes possible a small, wafer-thin tablet that acts within seconds, providing therapeutic pH adjustment almost immediately.

A NEW ADVANCE IN LIQUIDS, TOO... "RIOPAN" SUSPENSION

"RIOPAN" Suspension offers a welcome taste change—refreshingly cool, clean mint flavor with no aftertaste — and predictable buffering action, almost immediately providing a uniform, physiologic pH range in both large and small amounts of HCl, even with varying dosage.

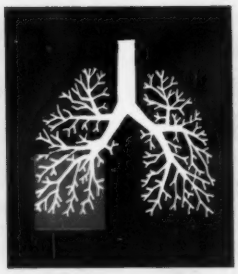
Dosage: 1 or 2 tablets **swallowed** with water as required, or 1 or 2 teaspoonfuls of suspension with water as required; preferably between meals and at bedtime.

NOTE: In peptic ulcer, and whenever continuous control of acidity is desired, many clinicians prefer to give antacid medication at **hourly** intervals throughout the day.

Supplied: "RIOPAN" Tablets, No. 790 — Each tablet contains 400 mg. Monalium hydrate (hydrated magnesium aluminate). Packages of 60 and 500 in individual film strips of 10 tablets.

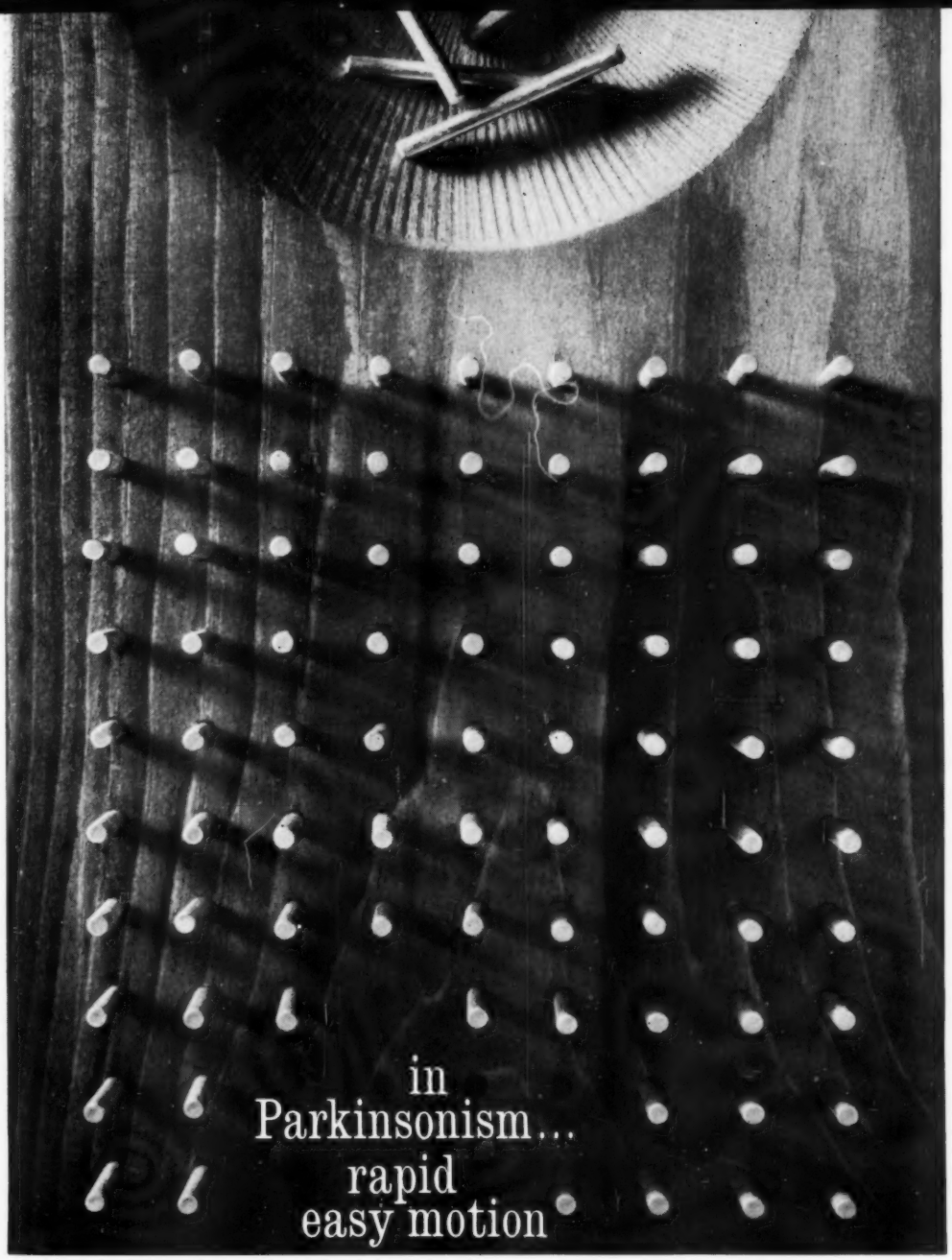
"RIOPAN" Suspension, No. 906 — Each teaspoonful contains 400 mg. Monalium hydrate (hydrated magnesium aluminate). Bottles of 12 fluidounces.

6117



when the allergy is more than antihistamines alone can control...and intensive steroid therapy alone is more than the allergy requires....

Lederle LEDERLE LABORATORIES



ARTANE helps restore a significant degree of function to the Parkinsonism patient. It also improves akinesia, offsets mental depression and controls oculogyria. **ARTANE** has remarkably low toxicity and is well suited for the greatest number of patients. It is highly effective in all types of Parkinsonism, and in controlling Parkinsonoid reactions to ataractic therapy. Supplied: Tablets, 2 mg. and 5 mg.; Elixir, 2 mg./5 cc. tsp.

ARTANE®

Trihexyphenidyl HCl Lederle

Request complete information on indications, dosage, precautions and contraindications from your Lederle Representative or write to Medical Advisory Department.

LEDERLE LABORATORIES • A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

Daricon®

OXYPHENCYCLIMINE HYDROCHLORIDE

anticholinergic with staying power

***1 TABLET P.M.**
usually assures nightlong freedom from pain by providing prolonged and sustained (8-12 hours') anticholinergic action that *combats nocturnal increase* in the basal gastric secretion of peptic ulcer patients

***1 TABLET A.M.**
usually assures uninterrupted daytime control of gastric hypersecretion without dependence on the repeat doses required of shorter-acting anticholinergics

Science for the world's well-being®

Pfizer

PFIZER LABORATORIES
Division,
Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

"wearability"

355 cc. (12 Ounces)
List No. 346
MAALOX®
RORER
(MAGNESIUM-ALUMINUM HYDROXIDE GEL)
ANTACID — DEMULCENT
NON-CONSTIPATING
A colloidal suspension of Magnesium and Aluminum Hydroxides useful for the relief of gastric hyperacidity.
Shake Well Before Using
Average adult dose: As antacid and protective, two to four teaspoonfuls may be given in water or milk twenty minutes after meals and at bedtime. Use as directed by your physician. Maalox should not be used in patients who are severely debilitated or suffering from kidney failure.
KEEP BOTTLE TIGHTLY CLOSED
KEEP FROM FREEZING
34772
WILLIAM H. RORER, Inc.
Pharmaceutical Chemists Philadelphia, Pa., U.S.A.

NO TASTE FATIGUE
EXCELLENT RESULTS
NO CONSTIPATION

the most widely prescribed and most wearable of all antacids

suspension tablets

Tablet Maalox No. 1 equivalent to 1 teaspoon Suspension

Tablet Maalox No. 2 equivalent to 2 teaspoons Suspension

when allergy looms large in the life of your patient...

BENADRYL provides a twofold therapeutic approach to the management of distressing symptoms of grass-pollen allergy ■ **antihistaminic action** relieves nasal congestion, sneezing, lacrimation, and pruritus ■ **antispasmodic action** affords relief of bronchial and gastrointestinal spasm.

BENADRYL Hydrochloride (diphenhydramine hydrochloride, Parke-Davis) is available in a variety of forms including: Kapseals® of 50 mg.; Capsules of 25 mg.; Emplets® (enteric-coated tablets) of 50 mg.; in aqueous solutions: 1-cc. Ampoules, 50 mg. per cc.; 10- and 30-cc. Steri-Vials,® 10 mg. per cc.; Elixir, 10 mg. per 4 cc.; 2% Ointment (water-miscible base); Kapseals of 50 mg. BENADRYL Hydrochloride with 25 mg. ephedrine sulfate. *Precautions:* Avoid subcutaneous or perivascular injection. Single parenteral dosage greater than 100 mg. should be avoided, particularly in hypertension and cardiac disease. Products containing BENADRYL should be used cautiously with hypnotics or other sedatives; if atropine-like effects are undesirable; or if the patient engages in activities requiring alertness or rapid, accurate response.

PARKE-DAVIS

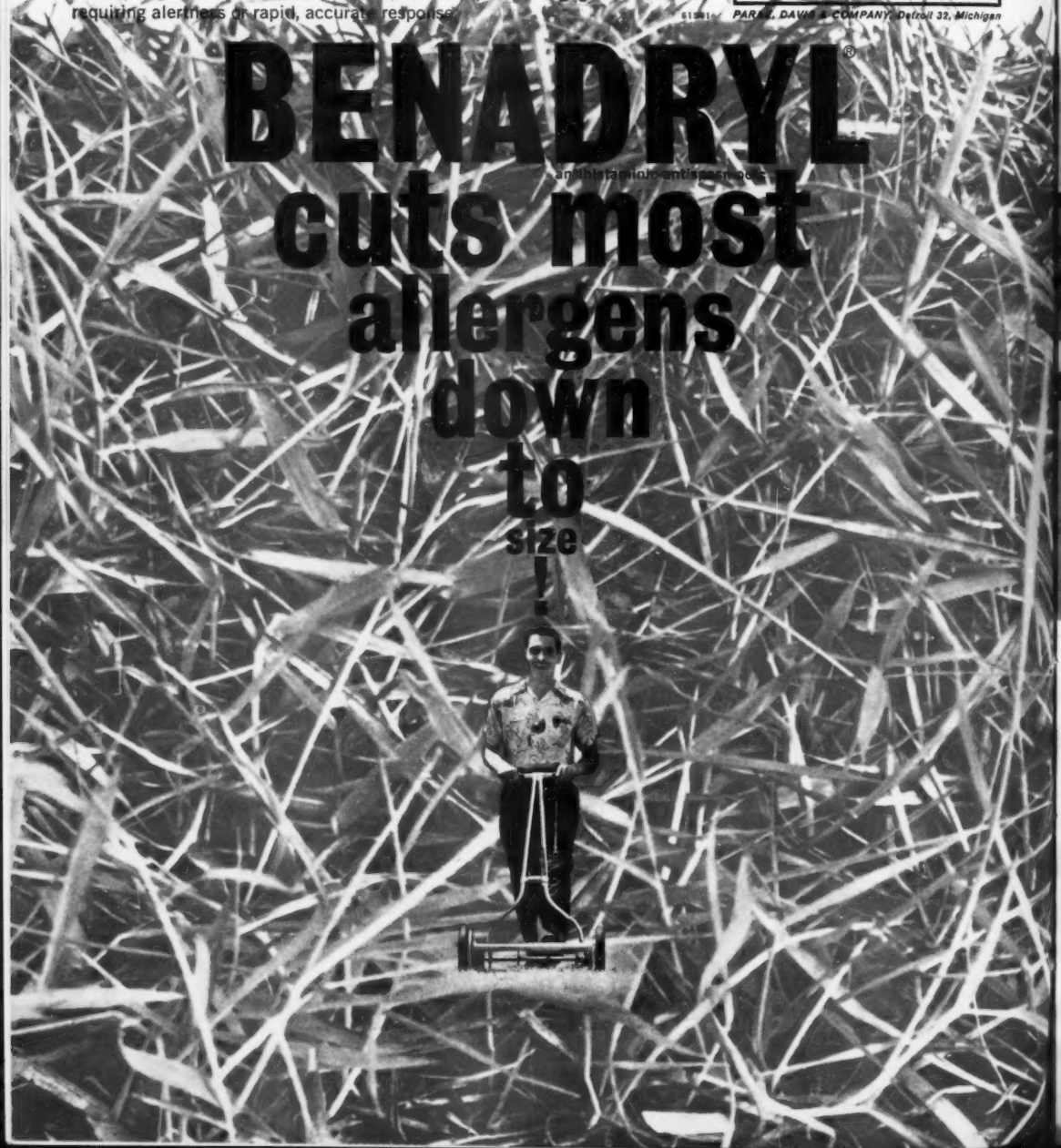
PARKE, DAVIS & COMPANY, Detroit 32, Michigan

61581-

BENADRYL®

antihistaminic-antispasmodic

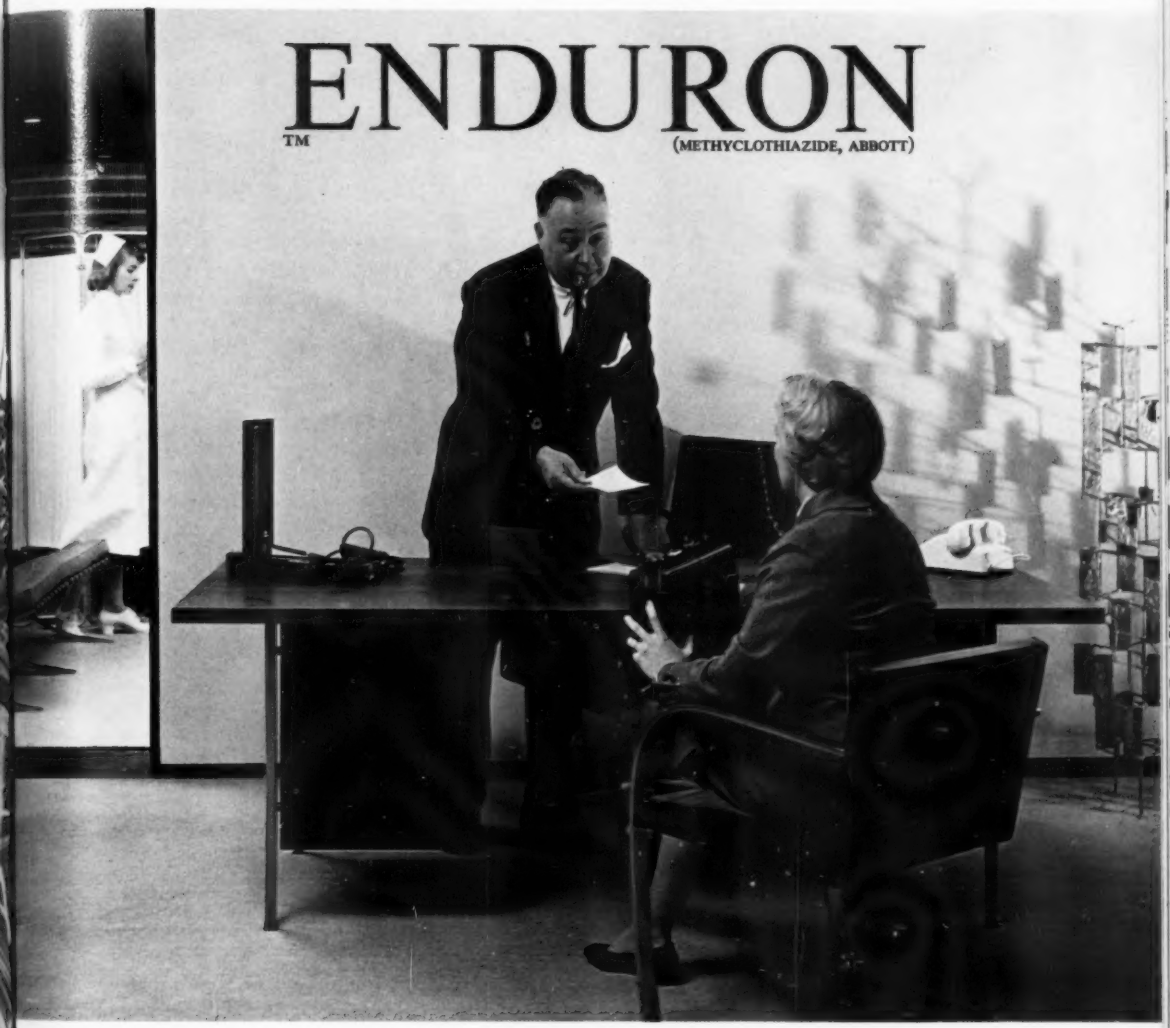
cuts most allergens down to size!



The 24-hour diuretic-antihypertensive

ENDURON™

(METHYCLOTHIAZIDE, ABBOTT)



Nothing is simpler in thiazide therapy: Prescribe "Enduron once a day, every day"

One dose daily of this potent new thiazide is ample. It treats edema and hypertension around the clock. You can expect therapeutic action through the full 24 hour period (and longer).

What's more, Enduron provides an enhanced potassium-sparing effect. Whereas multiple dose drugs may cause multiple peaks of potassium loss, Enduron's single dose brings but a temporary single peak.

Enduron's once-a-day dosage is of course a convenience, too. Easy for the patient to remember. Easy for you to supervise. We invite you to experience its benefits . . . soon. *(See next page)*

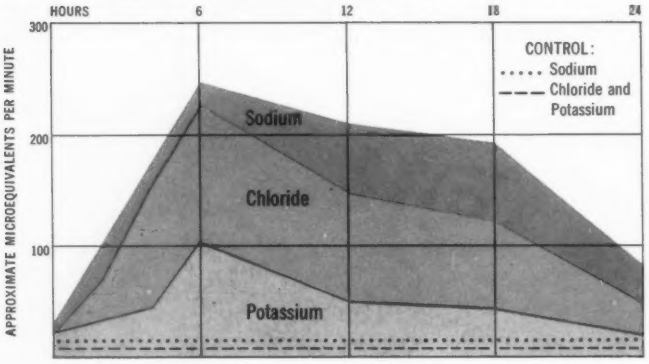
ABBOTT

104030A

Every ENDURON tablet delivers over 24 hours of continuous thiazide action

With this unique agent, you need just *one* daily dose to reduce edema and hypertension. Diuretic response reaches maximum in about six hours. It then follows a smooth, continuing plateau for most of the remaining day. Even at end of the 24 hours, you are still eliminating sodium well above control (i.e., undosed) amounts.

Usual Urinary Excretion Patterns Following 10 mg. of Enduron



Note that Enduron's effect on urinary potassium is minor; potassium depletion will seldom be a factor in your therapy. Similarly, Enduron's favorably high ratio of sodium versus chloride excretion means lessened likelihood of hypochloremic alkalosis.

How safe is Enduron?

Repeated oral doses of many thousand times the therapeutic amount, have been well tolerated in test animals for months. Since Enduron's milligram dosage in humans is low, it affords the security of an exceptionally safe therapeutic ratio.

Difficulty, if any, is apt to arise from therapy that's unnecessarily vigorous. Enduron is potent. 10 mg. produces at least as much sodium excretion as other available thiazides in *any* size dose. Single doses greater than 10 mg. don't accomplish greater diuresis, and aren't recommended or needed.

Prescribe the 24-hour diuretic-antihypertensive:

ENDURON

(METHYCLOTHIAZIDE, ABBOTT)

significant advance in thiazide therapy

ABBOTT

1. Ford, R. V., Current Therap. Res., 2:422-430, Sept., 1960.
2. Bryant, J. M., et. al., Current Therap. Res., 3:1-4, Jan., 1961.

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1040308

Psoriasis of 37 yrs' duration. Previous therapy produced no improvements.

Same Patient: Clearing after 2 mos' treatment with Lipan. Dosage: 5 capsules 3 times daily.

ACHIEVE FREEDOM FROM PSORIASIS w/LIPAN

Over and over again, studies have shown Lipan Improved Capsules to be orally effective therapy. Lipan will, in most cases, give a rapid clinical response. Maintenance dosage frequently keeps the patient symptom-free.

Again, in a recent study[1] on psoriatics of long standing, 37.71% showed complete remission of symptoms, 32.26% showed decided improvement, and 12.90% showed moderate or temporary improvement.

These new studies on the use of Lipan Improved Capsules have demonstrated that the clinical results are in direct proportion to adequate daily dosage.[2,3]

Effectiveness of Lipan therapy increases as dosage is increased.

Dosage: For complete *Lipanization* (saturation dosage): 2 to 4 capsules before each meal: 1 to 2 capsules before between-meal snacks.

Each Lipan Improved Capsule contains: Pancreatin – 2000 mg., Pyridoxine HCl – 3 mg.

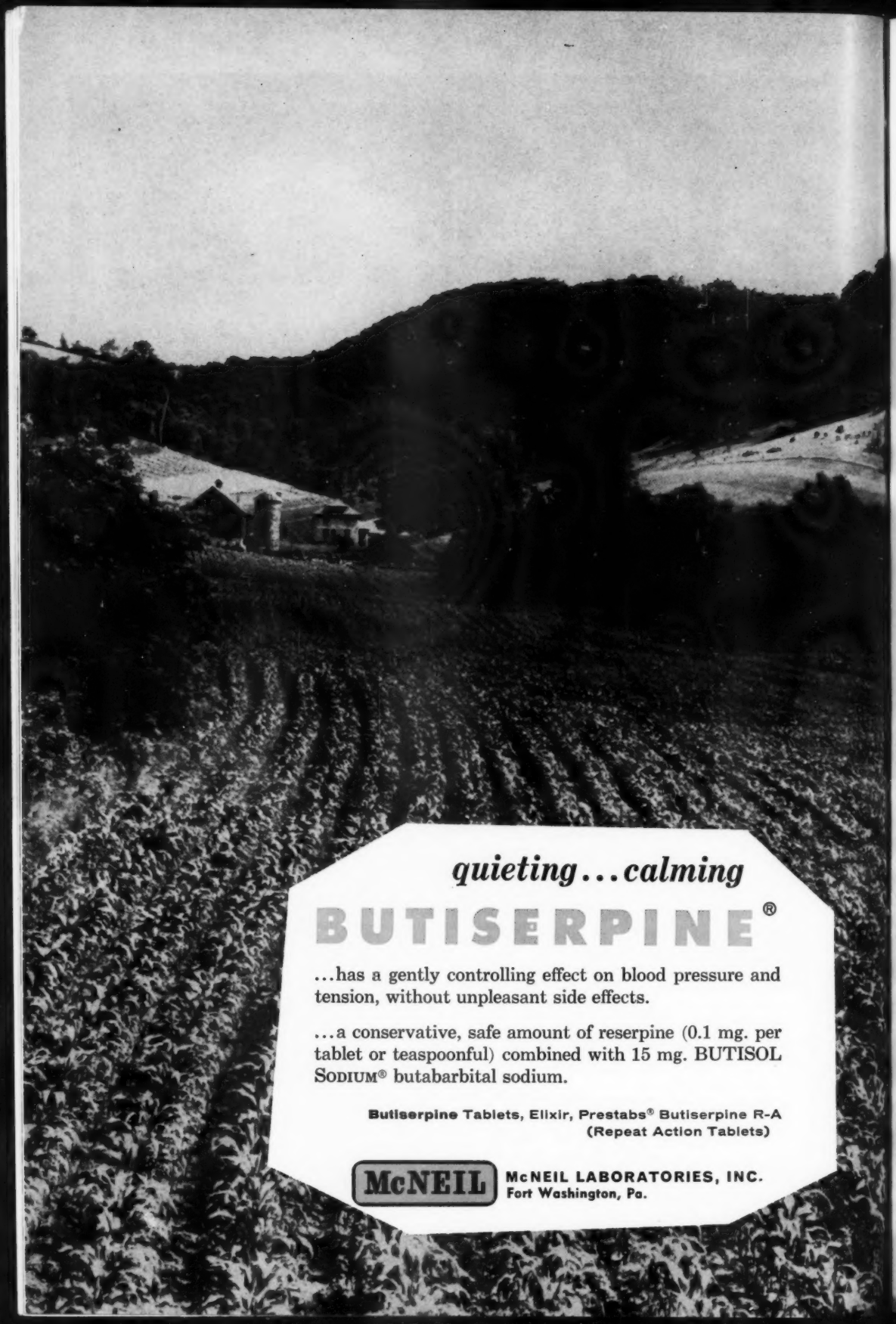
Reprints, Samples and Literature upon request

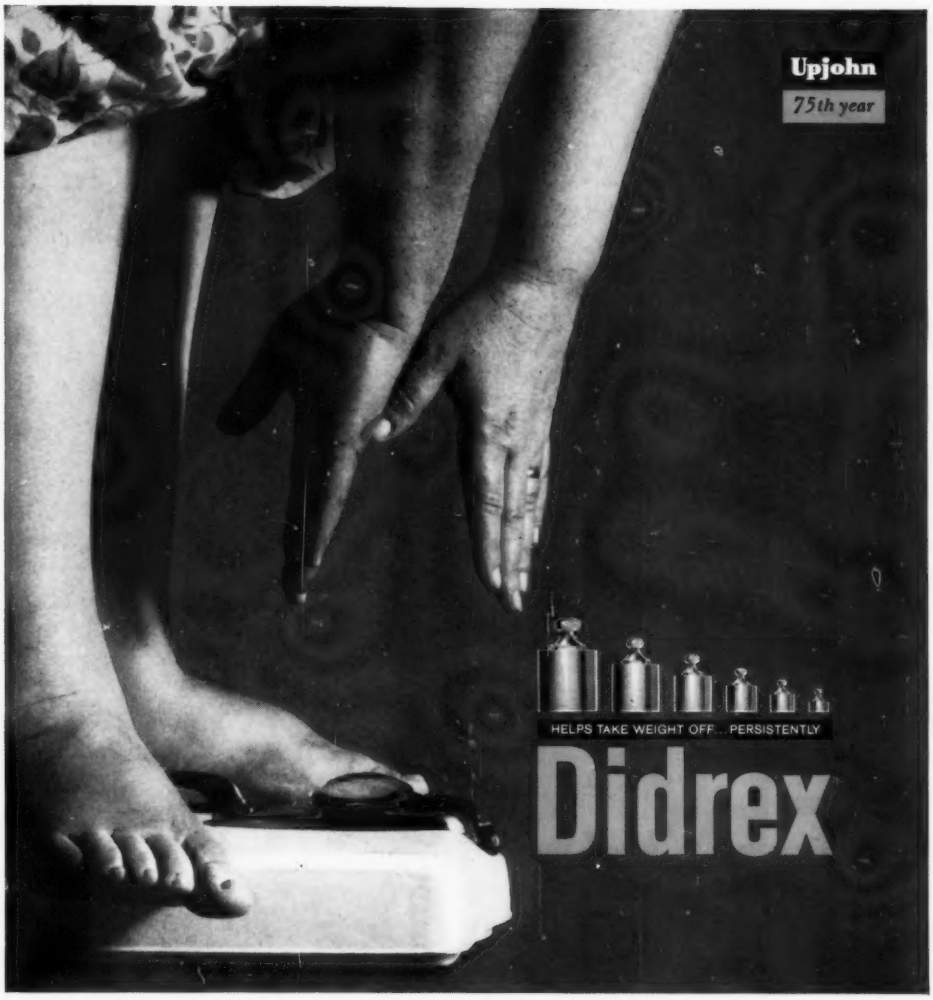
Spirt & Co., Inc.

Waterbury, Conn.

REFER TO PDR
PAGE 747

REFERENCES: 1. Schwartzschild, L.: Oral Management of Psoriasis with a Lipotropic Agent. Clin. Med., Vol. 8, No. 4, (April) 1961.
2. Combes, F. C.: Management of Psoriasis as a Metabolic Lipid Disturbance. N. Y. St. Jrl. Med., Vol. 54, No. 13, July 1, 1954.
3. Rosenthal, T.: Management of Psoriasis. Clin. Med., Vol. 7, No. 3, (March) 1960.


quieting...calming
BUTISERPINE®
...has a gently controlling effect on blood pressure and tension, without unpleasant side effects.
...a conservative, safe amount of reserpine (0.1 mg. per tablet or teaspoonful) combined with 15 mg. BUTISOL SODIUM® butabarbital sodium.
Butiserpine Tablets, Elixir, Prestabs® Butiserpine R-A (Repeat Action Tablets)
McNEIL
McNEIL LABORATORIES, INC.
Fort Washington, Pa.



Didrex doesn't perform miracles... it just helps the obese patient do it herself.

The reason is simple: persistent, significant loss of weight, up to 30 weeks in reported cases, helps to preclude the "weight plateau" that so often discourages dieters after a few weeks. Thus, time and will become your allies in changing the patient's dietary habits built over months or years of weight accumulation. Didrex may be used in closely supervised diabetic, coronary insufficient, and hypertensive patients.

BRIEF BASIC INFORMATION

Description: Didrex is the Upjohn brand of benzphetamine hydrochloride [(+)-N-benzyl-N, α-dimethyl-phenethylamine hydrochloride]. A sympathomimetic compound with marked anorectic action and relatively little stimulating effect on the CNS or cardiovascular system.

Indications: Control of exogenous obesity.

Contraindications: None known to date. However, use with caution in moderate or severe hypertension, thyrotoxicosis, acute coronary disease, or cardiac decompensation.

Dosage: Initiate appetite control with ½ to 1 tablet (25 to 50 mg.) in mid-morning or mid-afternoon, according to the patient's eating habits for several days. Then "adjust" dosage to suit each patient's needs to a maximum of 3 tablets daily (150 mg.).

Side Effects: No effects on blood, urine, renal or hepatic functions have been noted. Minimal side effects have been observed occasionally: dry mouth, insomnia, nausea, palpitations and nervousness.

Supplied: 50 mg., benzphetamine hydrochloride, press-coated, scored tablets, in bottles of 100 and 500.

*Trademark—brand of benzphetamine hydrochloride, Upjohn.

References: 1. Stough, A. R.: Weight loss without diet worry: use of benzphetamine hydrochloride (Didrex). Journal of the Oklahoma State Medical Association, 53:760-767 (November) 1960. 2. Oster, H., and Medlar, R.: A clinical pharmacologic study of benzphetamine (Didrex), a new appetite suppressant. Arizona Medicine, 17:398-404 (July) 1960. 3. Simkin, B., and Wallace, L.: A controlled clinical trial of benzphetamine (Didrex). Current Therapeutic Research, 2:33-38 (February) 1960.

essential
partners
in the
control
of edema

classic MERCUHYDRIN®

brand of meralluride sodium

nonmercurial METAHYDRIN®

brand of trichlormethiazide

Now...the alternate or combined use of these two drugs can help the physician meet with maximum efficiency the demands of diuretic therapy in almost any phase or degree of cardiac edema—acute or chronic.

SEND FOR METAHYDRIN BROCHURE

SUPPLIED:

METAHYDRIN—Tablets of 2 mg. and 4 mg. in bottles of 100 and 1000.

MERCUHYDRIN—1 cc. and 2 cc. ampuls in boxes of 12, 25 and 100, and 10 cc. rubber capped, multiple dose vials in boxes of 6, 25 and 100. Needs no refrigeration.

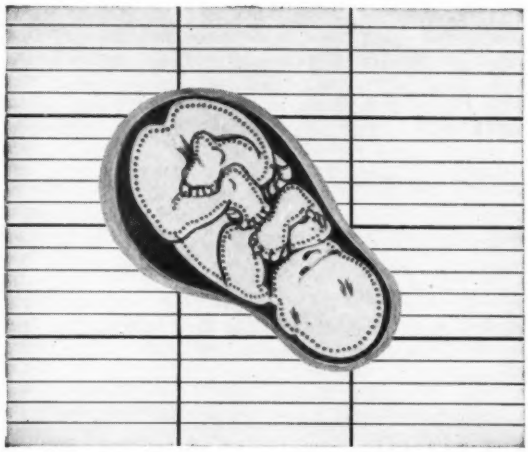
LAKESIDE

now in threatened premature delivery

Dactil®-OB

Brand of piperidolate hydrochloride, hesperidin complex and vitamin C

maintains gestation / increases fetal survival rate



"Dactil has been used as a preventive measure with great success and with no untoward effects."[1]

In a study of 618 pregnancies over a period of 4 years, premature births were reduced from 13.1% of 168 patients without Dactil to 4.7% of 450 patients with Dactil.[2] In the treated patients birth weights were increased.

Dosage: 1 tablet q.i.d. from the beginning of pregnancy in any patient with a history of previous difficulty. For more information send for Dactil-OB brochure.

(1) Stephens, L. J.: Prevention of Premature Delivery: Am. J. Obst. & Gynec. 70:6 (June) 1958. (2) Stephens, L. J., in press. 72561

LAKESIDE

There is an increasing awareness of iron deficiency in infants and children

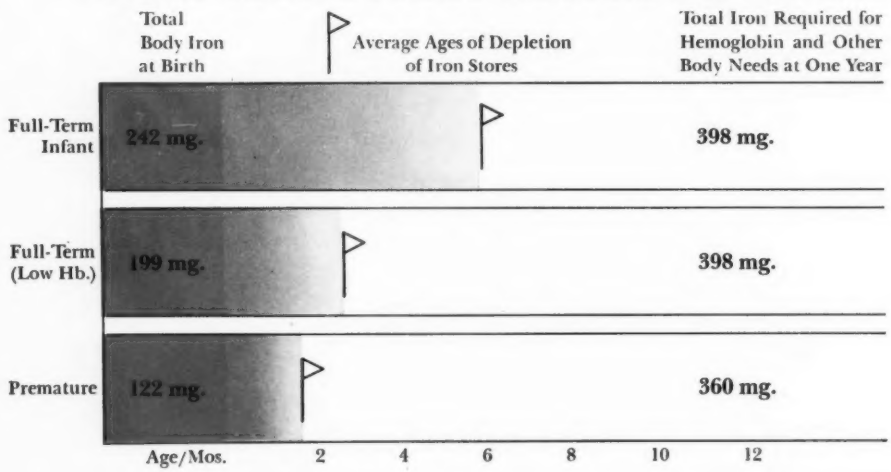
"Iron deficiency anemia is the most common deficiency disease of infancy and childhood."[1]

"The average full-term infant requires 8 mg. of iron daily from about 6 months of age...."[2]

The older child, too, often is in a precarious state of iron balance "...because of his added needs to support growth and his expanding blood volume...."[3]

The following chart shows the ages at which iron stores of the newborn infant tend to become depleted and the total iron needed by the end of the first year. To help fill the gap, prophylactic iron should be started at 2 to 6 months of age.

WHEN IRON STORES BECOME DEPLETED[2]



References: (1) Jacobs, I.: GP *21*:93 (Jan.) 1960. (2) Shulman, I.: J.A.M.A. *175*:118-123 (Jan. 14) 1961. (3) Moore, C. V., in Wohl, M. G., and Goodhart, R. S.: Modern Nutrition in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1960, p. 243.

Mead Johnson Laboratories

Symbol of service in medicine

Now...two new products to supply the iron they need at the ages they need it

TRI-VI-SOL®

VITAMIN DROPS WITH IRON

DECA-VI-SOL®

CHEWABLE VITAMINS WITH IRON

These two new formulations—one for infants, one for older children—are distinctive additions to the present line of Vi-Sol® vitamins, thereby providing the choice of Tri-Vi-Sol drops with and without iron and Deca-Vi-Sol chewable vitamins with and without iron. Both new products taste good. The packaging carefully limits elemental iron to a total of 500 mg. per bottle. Nevertheless, the bottles should be kept out of the reach of children.

Tri-Vi-Sol vitamin drops with iron. **Each 0.6 cc. daily dose supplies 10 mg. elemental iron plus safe, rational amounts of vitamins C, D and A. Supplied in bottles of 30 cc.**

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10 mg. of prophylactic iron... logically combined for your convenience with two of the most widely used and accepted pediatric vitamin products

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achievement in
corticosteroid
research

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(*paramethasone acetate, Lilly*)

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predictable
anti-inflammatory
effect

Haldrone is a potent synthetic corticosteroid with marked anti-inflammatory activity. In steroid-responsive conditions, it provides predictable anti-inflammatory effects with a minimum of untoward reactions. Gratifying response has been observed in patients transferred from other corticosteroids to Haldrone. There is relatively little adverse effect on electrolyte metabolism. With Haldrone, sodium retention is unlikely, psychic effects are minimal, and there appears to be freedom from muscle weakness and cramping.

Haldrone, 2 mg., is approximately equivalent to

Cortisone	25 mg.
Hydrocortisone	20 mg.
Prednisone or prednisolone	5 mg.
Triamcinolone or methylprednisolone	4 mg.
Dexamethasone	0.75 mg.

Although the incidence of significant side-effects is low, the usual contraindications to corticosteroid therapy apply to Haldrone.

Supplied in bottles of 30, 100, and 500

Tablets Haldrone, 1 mg., Yellow (scored)
Tablets Haldrone, 2 mg., Orange (scored)

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Gastro-intestinal disorders?

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Diarrheas, dysenteries—many other intestinal disorders—respond quickly and favorably to pharmaceutical specialties whose key ingredient is *an adequate dosage* of citrus pectin or a derivative.

Sunkist® Pectin N.F. provides a dependable therapeutic dosage of galacturonic acid—the recognized detoxicating factor. Specialty formulations of leading pharmaceutical manufacturers contain this product of Sunkist Growers.

Literature and bibliography is available. Address: Sunkist Growers, Pharmaceutical Products, 720 East Sunkist Street, Ontario, Calif.

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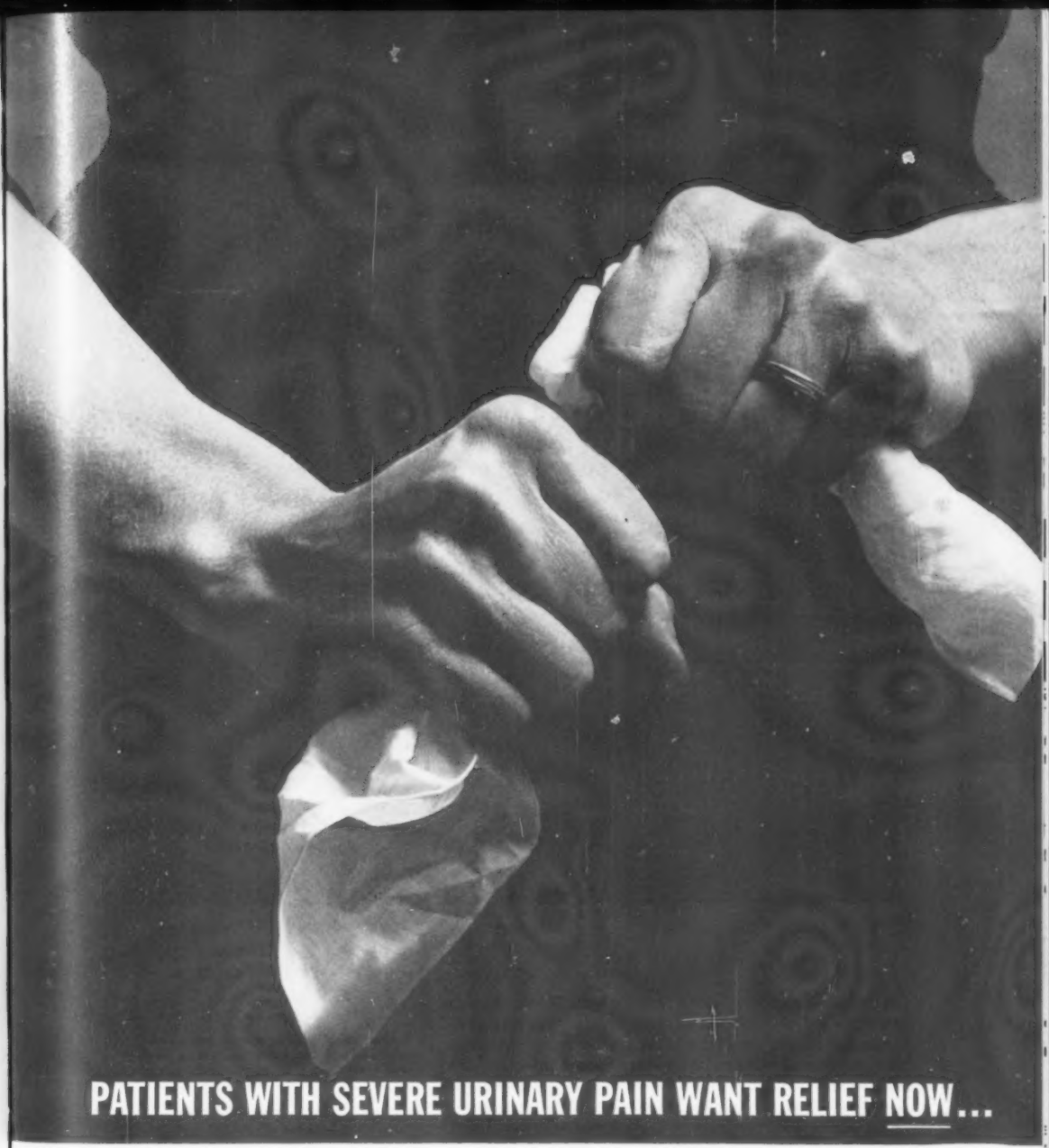

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Two Pyridium tablets t.i.d. relieve the pain of urinary infection in only 30 minutes. During the first 3 to 4 days of therapy, Pyridium, prescribed along with any antibacterial of your choice, will make your patient comfortable until the antibacterial reduces inflammation and controls the infection.

AVERAGE DOSE: Adults—2 tablets t.i.d. Children 9 to 12 —1 tablet t.i.d. SUPPLIED: 0.1 Gm. tablets, bottles of 50. PRECAUTIONS: Pyridium is contraindicated in patients with renal insufficiency and/or severe hepatitis. *Full dosage information, available on request, should be consulted before initiating therapy.*

WARNER CHILCOTT

MORRIS PLAINS, N.J.

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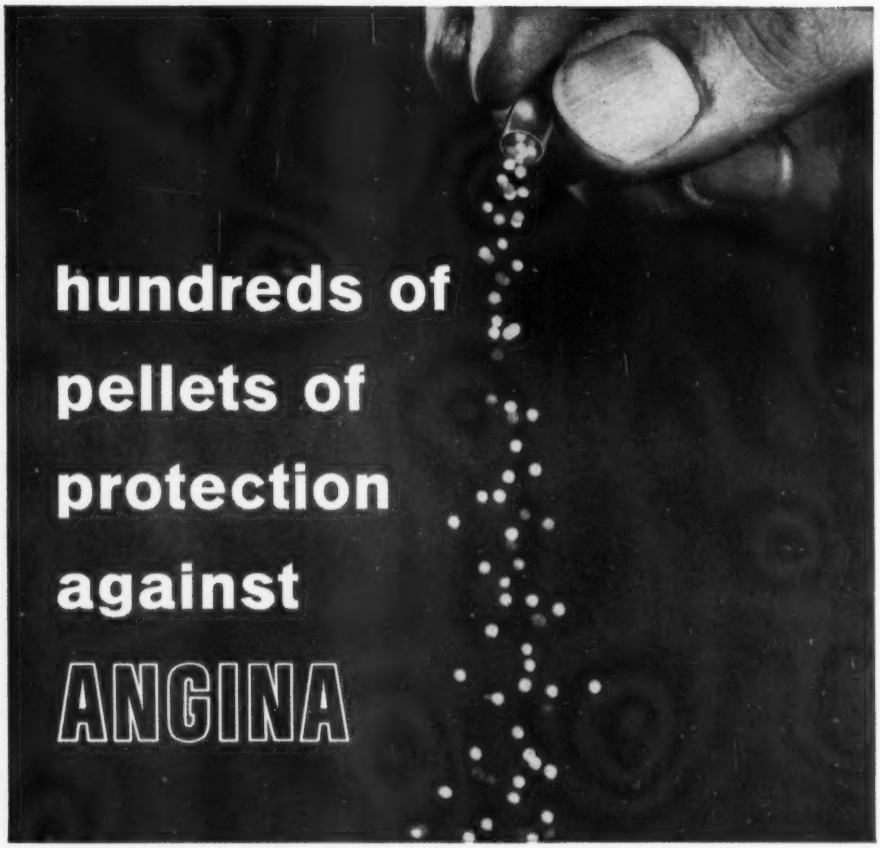
makers of TEDRAL GELUSIL PROLOID PERITRATE MANDELAMINE



PENTRITOL® TEMPULES

controlled disintegration capsules

A single 30 mg. Pentritol Tempule with 12 hour action exhibits an even nitrite release which "tends to produce a smooth, prolonged response similar to that of the sustained release of modern depot injections."[1] Duration, frequency, and severity of anginal attacks are markedly lessened. Patients showing little progress during years of therapy with 80 mg. daily of PETN tablets, respond favorably to the smaller dose of Pentritol Tempules.[2] Kamil and Klinger report the response of their patients to a timed-disintegration pentaerythritol tetranitrate capsule as excellent, with nitroglycerin requirements reduced as much as 85%.[3]

1. Biegeleisen, H. I.: Clin. Med. *2*:1005, 1955. 2. Roberts, J. T.: Clin. Med. *4*:1375, 1957. 3. Kamil, M., and Klinger, I.: New York State J. Med. *59*:3398, 1959.

PENTRITOL

Each Pentritol Tempule is a controlled disintegration capsule containing 30 mg. of pentaerythritol tetranitrate in granular form. An initial dose of 10 mg. is released at once; a second dose 4 hours later; and a third dose 8 hours after ingestion. Thus, each Tempule affords at least 12 hours of coronary vasodilation. ACTION AND USES: Effective therapy for and prophylaxis against anginal attacks. One Tempule morning and evening will provide 24 hours of effective medication, with a smooth, sustained clinical effect that has shown superior results. Pentritol reduces or eliminates nitroglycerin requirements, stops or reduces frequency of anginal attacks, eliminates or mitigates pain, and increases capacity for physical activity. CONTRAINDICATIONS: Observe caution in glaucoma. DOSAGE: One Pentritol Tempule morning and evening, approximately 12 hours apart. SUPPLIED: Bottles of 60 and 250. Also available: Pentritol®-B Tempules®, with 30 mg. pentaerythritol tetranitrate and 50 mg. butabarbital, for 12 hours of coronary vasodilation plus sedation.

ARMOUR PHARMACEUTICAL COMPANY
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your episiotomy patient is entitled to

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STREPTOKINASE-STREPTODORNASE LEDERLE

buccal tablets

for a faster recovery with more comfort

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

when
he's
ready
for
cereals...

PABLUM®
BRAND

your
guidance
is
still
important

Mother looks for your guidance

"Cereal is an excellent food to offer the baby who has a large appetite early in life and is not satisfied with the calories provided by his intake of milk."[1] When to start and what cereal to choose for baby? These are important questions for a mother. Your guidance is as important now as when you prescribed baby's first formula.

Five tasteful varieties—Rice, Mixed, Oatmeal, Barley and High Protein—help with important taste-training and feeding patterns. In addition to calories, PABLUM Cereals provide protein, carbohydrate, vitamins, and important minerals—especially iron. They are formulated especially to help meet the infant's nutritional needs when he graduates to solid foods.

Baby needs your guidance

Because rice is hypoallergenic,[2] PABLUM Rice Cereal is well suited to the allergic infant.

PABLUM High Protein Cereal is useful when the diet requires added protein. It has been noted that "addition of PABLUM to infants' diets considerably increased the amount of fluorine ingested"[3]—an important consideration for caries prevention.

When you specify PABLUM, you are sure of safe, sound, nutritious cereals for baby's early years.

Specified by physicians for nearly 30 years.

References: (1) Bartram, J. B., in Nelson, W. E.: Textbook of Pediatrics, ed. 7, Philadelphia, W. B. Saunders Company, 1959, p. 128. (2) Benson, R. A., and Kimball, F. T.: Arch. Pediat. *64*:476, 1947. (3) Ham, M. P., and Smith, M. D.: J. Nutrition *53*:215, 1954.

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in strains or sprains

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buccal tablets

can make a difference to your patient/ reduce recovery time/add comfort to convalescence

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

not a general-purpose antibiotic

Albamycin is not a broad-spectrum antibiotic, recommended for routine infections. It is specific for staphylococci (including resistant strains), and its use alone should (with the exceptions listed below) be limited to those cases in which staph is known or strongly suspected to be the causative organism.

Albamycin*

Indications — Albamycin is indicated in the treatment of staphylococcic infections, particularly in patients sensitive to other antibiotics or in the infections in which the organism is resistant to other antibiotics and sensitive to Albamycin, and in urinary tract infections due to microorganisms resistant to other commonly employed antibacterial agents but sensitive to Albamycin — notably certain strains of Proteus.

Administration and Dosage — Capsules and Syrup: The recommended dosage in adults is 500 mg. every twelve hours or 250 mg. every six hours, continued for at least forty-eight hours after the temperature has returned to normal and all evidence of infection has disappeared. In severe or unusually resistant infections, 0.5 Gm. every six hours or 1 Gm. every twelve hours may be employed. The dose for children is 15 mg. per kilogram of body weight per day for moderately acute infections; this may be increased to 30 to 45 mg. per kilogram of body weight per day for severe infections. These doses may be administered on schedules similar to those for adults.

Parenteral: Intramuscularly—5 cc. of Albamycin solution may be used directly by slow injection deep into the gluteal muscle.

Intravenously — it is recommended that 5 cc. of Albamycin solution be diluted further with 250 to 1000 cc. of sterile injection solution of sodium chloride, Darrow's solution, or Ringer's solution and administered by intravenous infusion, or by diluting to a suitable quantity and administered by continuous drip infusion.

Do not use with dextrose solution. When it is necessary to use a smaller volume intravenously, 5 cc. of Albamycin solution may be diluted to a minimum of 30 cc. with one of the above diluents and administered slowly over a period of five to ten minutes to avoid irritation of the vascular endothelium. The dosage for adults is 500 mg. Albamycin administered either intramuscularly or intravenously every twelve hours. For children with moderately acute infections, the dosage is 15 mg. per kilogram of body weight per day. The daily dosage should be administered in two divided doses at intervals of twelve hours. As soon as the patient's condition permits, parenteral Albamycin should be replaced with oral Albamycin therapy.

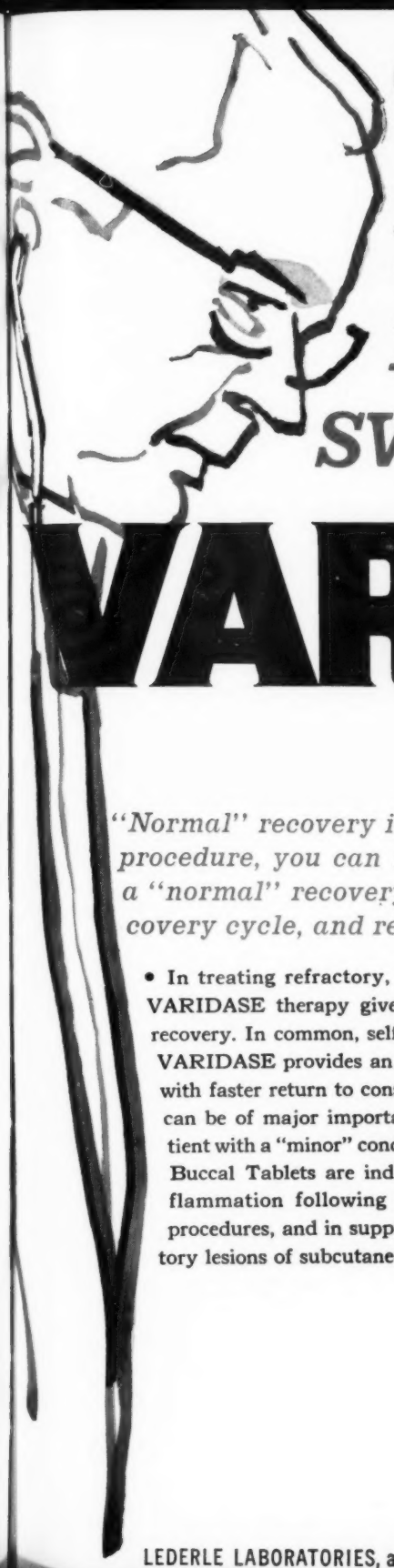
Side Effects — Albamycin is a substance of low toxicity but is capable of inducing urticaria and maculopapular dermatitis. Leukopenia, which was rapidly reversible, has been reported in approximately 1% of cases. All of these side effects disappear rapidly upon discontinuance of the drug. In a certain few patients, a yellow pigment has been found in the plasma. This pigment is a metabolic by-product of the drug which, however, may interfere with determination of bilirubin and icteric index. Its presence is not associated with abnormal liver function tests or liver enlargement.

Available — Albamycin, 500 mg., sterile, Mix-O-Vial.† Each Mix-O-Vial contains: 500 mg. Novobiocin (as novobiocin sodium), also 175 mg. Nicotinamide; 0.47 cc. N,N-Dimethylacetamide; 42.3 mg. Benzyl alcohol; 4.23 cc. water for injection. Albamycin Capsules. Each capsule contains: 250 mg. Novobiocin (as novobiocin sodium). Albamycin Syrup. 125 mg. per 5 cc. Each 5 cc. (one teaspoonful) contains: 125 mg. Novobiocin (as novobiocin calcium). Preserved with methylparaben, 0.075%, and propylparaben, 0.025%.

*Trademark, Reg. U. S. Pat. Off. — The Upjohn brand of crystalline novobiocin sodium. †Trademark, Reg. U. S. Pat. Off.

The Upjohn Company
Kalamazoo, Michigan

Upjohn



do all you can whenever there is local inflammation/ swelling/pain...

VARIDASE

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buccal tablet

"Normal" recovery is not enough. Now, by adding VARIDASE to you procedure, you can release your patient from the stress and pain a "normal" recovery—put comfort in convalescence, shorten the r covery cycle, and reap the reward of greater patient appreciation.

• In treating refractory, chronic conditions, VARIDASE therapy gives added impetus to recovery. In common, self-limiting conditions, VARIDASE provides an easier convalescence with faster return to constructive living. This can be of major importance even to the patient with a "minor" condition. • VARIDASE Buccal Tablets are indicated to control inflammation following trauma or surgical procedures, and in suppurative or inflammatory lesions of subcutaneous and deep tissues.

• Precautions: VARIDASE has no adve effect on normal blood clotting. Care should taken in patients on anticoagulants or with a d cient coagulation mechanism. When infection present, VARIDASE Buccal Tablets should given in conjunction with antibiotics.

• Dosage: *One buccal tablet four times da usually for five days. To facilitate absorpti patient should delay swallowing saliva.*

• Supplied: *Each tablet contains 10,000 Un Streptokinase, 2,500 Units Streptodornase. Bo of 24 and 100 Tablets.*

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

now...prolonged antipruritic action
in a chewable tablet
for chickenpox
and other pruritic conditions

new...unique...pleasant-tasting

tacaryl T.M.

chewable tablets

METHDILAZINE, MEAD JOHNSON

prolonged antipruritic/antiallergic action...
not dependent on delayed intestinal release

Itching in children can now be controlled on b.i.d. dosage with a long-acting[1] antipruritic/antiallergic chewable tablet your pediatric patients will enjoy taking.

Tacaryl Hydrochloride is exceptionally valuable in alleviating many types of allergic and non-allergic pruritus. For example, in a group of children, 2 to 12 years of age, with atopic dermatitis, chickenpox, or contact dermatitis, 80 per cent obtained substantial or complete relief of their itching when treated with Tacaryl Hydrochloride. "No patient in this age group failed to show some degree of improvement."[2]

Tacaryl Hydrochloride is also effective in controlling symptoms in a wide variety of allergic conditions,[2-8] including hay fever and perennial rhinitis.

dosage: One Chewable Tablet (3.6 mg.) twice daily. Adjustment of dose or interval may be desirable for some patients.

contraindications: There are no known contraindications.

side effects: Drowsiness has been observed in a small percentage of patients. Dizziness, nausea, headache, and dryness of mucous membranes have been reported infrequently.

cautions: If drowsiness occurs after administration of Tacaryl Chewable Tablets or Tacaryl Hydrochloride, the patient should not drive a motor vehicle or operate dangerous machinery. Since Tacaryl Chewable Tablets or Tacaryl Hydrochloride may display potentiating properties, it should be used with caution for patients receiving alcohol, analgesics or sedatives (particularly barbiturates). Because of reports that phenothiazine derivatives occasionally cause side reactions such as agranulocytosis, jaundice and orthostatic hypotension, the physician should be alert to their possible occurrence...though no such reactions have been observed with Tacaryl Chewable Tablets or Tacaryl Hydrochloride.

supplied: Pink tablets, 3.6 mg., bottles of 100.

references: (1) Lish, P. M.; Albert, J. R.; Peters, E. L., and Allen, L. E.: Arch. internat. pharmacodyn. *129*:77-107 (Dec.) 1960. (2) Howell, C. M., Jr.: North Carolina M. J. *21*:194-195 (May) 1960. (3) Clinical Research Division, Mead Johnson & Company. (4) Wahner, H. W., and Peters, G. A.: Proc. Staff Meet. Mayo Clin. *35*:161-169 (March 30) 1960. (5) Crepea, S. B.: J. Allergy *31*:283-285 (May-June) 1960. (6) Crawford, L. V., and Grogan, F. T.: J. Tennessee M. A. *53*:307-310 (July) 1960. (7) Spoto, A. P., Jr., and Sieker, H. O.: Ann. Allergy *18*:761-764 (July) 1960. (8) Arbesman, C. E., and Ehrenreich, R.: New York J. Med. *61*:219-229 (Jan. 15) 1961.

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CAROTID ARTERIAL INSUFFICIENCY— *SURGICAL CORRECTION*

Radiograph on Kodak Blue Brand X-ray Film; surgery photographed on Kodak Ektachrome Film

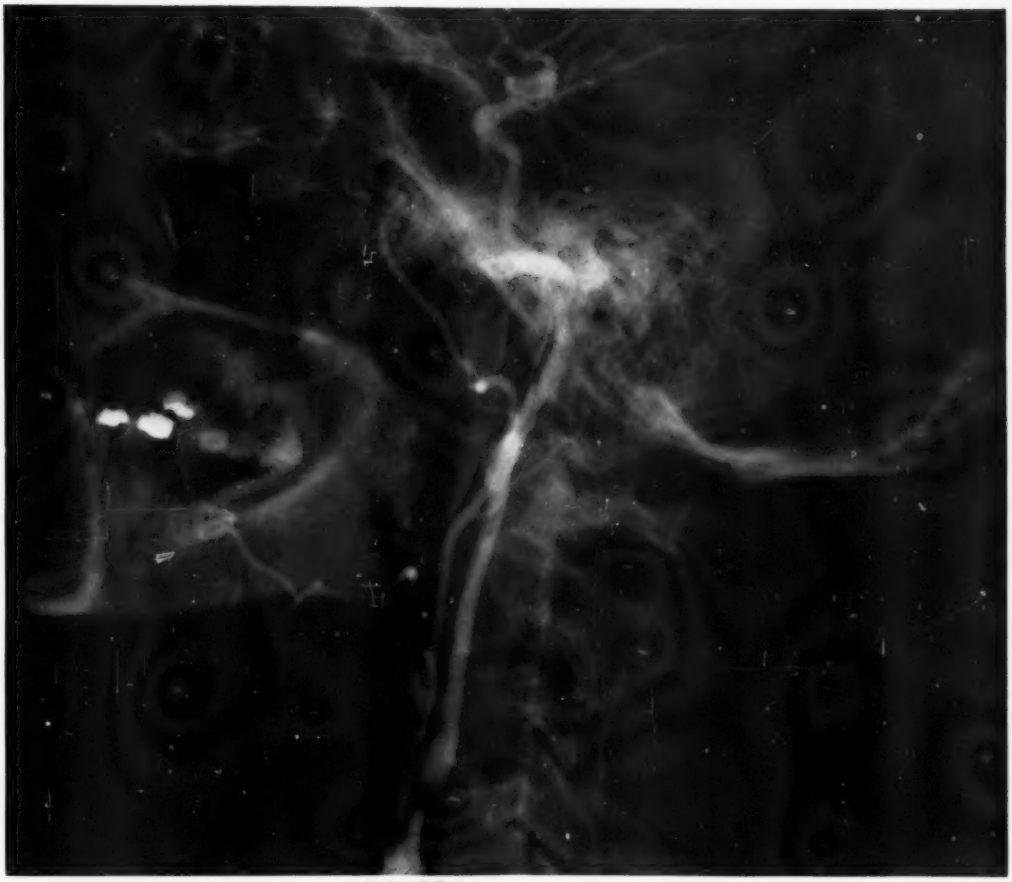

FIGURE 1.

Six steps in the surgical treatment. First, what the radiologist *saw:* next, what the surgeon *did.* Radiographs and photographs together provide a clear, objective record—basis for lectures, discussions and papers.

From original Kodak Ektachrome Film transparencies such as those reproduced here, slides, prints, black-and-white or color, may be obtained —invaluable today, tomorrow, years from now, yet obtainable at relatively small cost.

FIGURE 2.

Figure 1: Preoperative carotid arteriogram shows carotid arteries with sclerotic narrowing of the internal carotid artery at its origin. **Figure 2:** Incision along anterior border of the sternocleidomastoid muscle.

CAROTID ARTERIAL INSUFFICIENCY— *SURGICAL CORRECTION* (cont'd)

FIGURE 3.

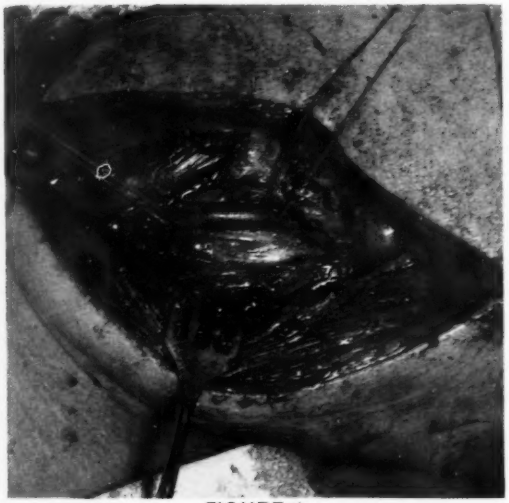

FIGURE 4.

FIGURE 5.

FIGURE 6.

Figure 3: Retraction of sternocleidomastoid muscle exposes deep cervical fascia. (Parotid gland now visible at upper pole of incision.) **Figure 4:** Tapes in place about internal jugular vein. **Figure 5:** Tapes around the carotid arteries. **Figure 6:** Internal carotid artery open and arteriosclerotic "core" being removed. *Note how effectively color establishes tissue differentiations.*

For Medical X-ray Film: Look to Kodak for highest quality medical x-ray film—Kodak Blue Brand and Kodak Royal Blue, Kodak's fastest x-ray film.

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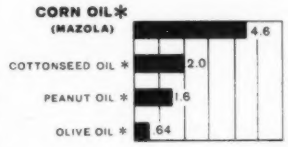

*U. S. Dept. of Agriculture Reports—1959

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Mazola Corn Oil has the following average composition:

Fatty Acids	Grams/ 100 grams	Grams/ fl. oz. (2 tablespoons)
Polyunsaturates...	52-58	14-15.7
Monounsaturates..	28-36	7.5-9.7
Saturates	10-14	2.8-3.8
Natural Sitosterols...	1 (0.9-1.3)	0.14
Natural Tocopherols..	about 0.1	0.015
Cholesterol	none	none
Salt (Sodium chloride)	none	none

Calories—125/tablespoon
Iodine value—124 average

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Now arthritic flare-ups can be controlled with much lower steroid dosages

With Somacort to relax muscles and relieve pain, tender joints need far less steroid to reduce inflammation

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Soma, by itself, benefits many arthritics by relieving the muscle spasm and pain which arise from joint inflammation. Thus with Somacort, which combines Soma with prednisolone, the amount of steroid needed to control inflammation[1] can be kept within more conservative limits.

Somacort is well tolerated even when used for long-term therapy in more serious cases.

1. Wein, A. B.; The Use of Carisoprodol (SOMA) in Orthopedic Surgery and Rehabilitation, Miller, James G., ed., Wayne State University Press, Detroit, Michigan, 1959.

Recommended dosage: 1 or 2 tablets q.i.d. (Each tablet contains 350 mg. carisoprodol, 2 mg. prednisolone)

SOMACORT™

(carisoprodol, Wallace, with prednisolone)

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PMB combines the effective calmative action of meprobamate, together with "Premarin," the most widely prescribed natural oral estrogen for specific control of menopausal symptoms.

PMB tranquilizes the overanxious and nervous patient, while "Premarin" gives prompt relief of distressing symptoms, imparts a "sense of well-being" and, in addition, exerts a protective influence in many vital processes as in cardiovascular, bone and protein metabolism.

Usual dosage: PMB ("Premarin" with Meprobamate)—one tablet 3 times daily. Dosage is adjusted to individual requirements. Cyclic therapy is recommended (3 week regimen with 1 week rest period) to avoid continuous stimulation of breast and uterus.

Caution: Meprobamate may produce drowsiness in some patients, but this usually disappears with continued therapy or reduced dosage. Severe allergic reactions are rare, but if they occur, this calls for immediate withdrawal of drug and treatment (epinephrine, antihistamines, or hydrocortisone).

Availability: No. 880—PMB-200—Each tablet contains 0.4 mg. conjugated estrogens, equine ("Premarin") and 200.0 mg. meprobamate. No. 881—PMB-400—Each tablet contains 0.4 mg. conjugated estrogens, equine ("Premarin") and 400.0 mg. meprobamate. (Both products in bottles of 60 and 500.)

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to combat the three-pronged assault of urinary tract infections *— bacteriuria — tissue infection — discomfort*

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COSA-TERRAMYCIN®—SULFONAMIDE—ANALGESIC

Only UROBIOTIC *contains:* OXYTETRACYCLINE (with glucosamine for enhanced absorption) — notable for its wide tissue distribution, high urinary concentration, excellent toleration and proven antibiotic effectiveness against even so troublesome an invader as *Pseudomonas;* SULFAMETHIZOLE — an unusually soluble, highly active sulfonamide; PHENYLAZO-DIAMINO-PYRIDINE — for effective local analgesia.

IN BRIEF

INGREDIENTS: Each Urobiotic capsule contains 125 mg. Terramycin® (oxytetracycline) with 125 mg. glucosamine HCl, 250 mg. sulfamethizole, and 50 mg. phenylazo-diamino-pyridine HCl.

INDICATIONS: Urobiotic is indicated in the treatment of a number of common genitourinary infections caused by susceptible organisms. It may also be used prophylactically before and after genitourinary or pelvic surgery, following instrumentation procedures, during the use of retention catheters, and in patients with conditions such as cord bladder or cystocele.

DOSAGE: In adults, a dose of 1 or 2 capsules four times daily is suggested, depending upon the severity and response of the infection. In children 60 to 100 lbs., the suggested average dose is 1 capsule four times daily; in children under 60 lbs., 1 capsule three times daily. Therapy should be continued for a minimum of 7 days or until bacteriologic cure is effected in acute urinary tract infections.

CONTRAINDICATIONS: Urobiotic may be contraindicated in patients with chronic glomerulonephritis, hepatitis, hepatic failure, uremia, and obstructive lesions of the urinary tract, and should not be used in patients sensitive to any of its components.

PRECAUTIONS: The use of broad-spectrum antibiotics may, in rare cases, result in an overgrowth of nonsusceptible organisms, such as monilia or staphylococci. Should such superinfection occur, therapy with Urobiotic should be discontinued and specific therapy instituted as shown by susceptibility testing. The use of sulfonamides may cause renal crystalluria or skin rash, as well as other toxic or sensitivity reactions. If any of these occur, discontinue use.

SUPPLIED: Urobiotic capsules, yellow-and-grey, bottles of 50.

Pfizer

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oral
fulvicin®
griseofulvin

Supplied: FULVICIN Tablets (scored), 500 mg., in bottles of 20 and 100; 250 mg., in bottles of 30, 100 and 500. *Reference:* Sulzberger, M. B., *et al.:* Dermatology: Diagnosis and Treatment, ed. 2, Chicago, Year Book Publishers, 1961, p. 350. For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, N. J.

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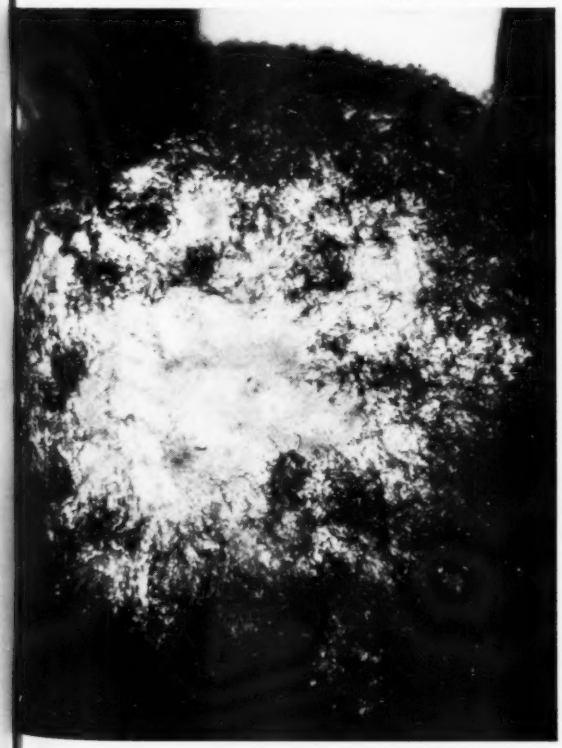

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NACTON® 4 mg. (poldine methylsulfate†) — new inhibitor of gastric acid secretion and hypermotility "... reduces the total output of gastric HCl by about 60%"[1]

plus

BUTISOL SODIUM® 15 mg. (butabarbital sodium) — "daytime sedative" with highest therapeutic index[2] (highly effective, minimal side effects)
smooth, predictable sedation of *6 hours' duration*

Side effects with NACTISOL therapy have been minimal.[3-5]

NACTISOL*...in scored, yellow tablets—bottles of 100

Typical gastric secretory gland.

a —chief cell (pepsin-producing).

b —parietal cell (acid-producing).

NACTISOL INHIBITS GASTRIC ACID SECRETION AT THE PARIETAL CELL* LEVEL

References

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2. Batterman, R. C., Grossman, A. J., Leifer, P., and Mouratoff, G. Clinical Re-evaluation of Daytime Sedatives, Postgrad. Med. *26*:502-5 (October) 1959.
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5. Rider, J. A.: Clinical Report to McNeil Laboratories.

McNEIL McNEIL LABORATORIES, INC., Fort Washington, Pa.

*Trademark
†U. S. Paten

objective:

full term fetus

complication:

threatened abortion

indicated:

Provera

Upjohn

Here are five reasons why:

- Provera is the only commercially-available oral progestational agent that will maintain pregnancy in critical tests in ovariectomized animals.
- It is four times as potent (by castrate assay) as any other progestational agent.
- No significant side effects have been encountered.
- It is available for both oral and parenteral administration
- Provera gives the economy of effective action from small doses.

Brief Basic Information

	● Oral Provera*	← I.M. Depo-Provera**
Description	Upjohn brand of medroxyprogesterone acetate.	Aqueous suspension, 50 mg. Provera per cc., for intramuscular injection only.
Indications	Threatened and habitual abortion, infertility, dysmenorrhea, secondary amenorrhea, premenstrual tension, functional uterine bleeding.	Threatened and habitual abortion, endometriosis.
Dosage Threatened abortion	10 to 30 mg. daily until acute symptoms subside.	50 mg. I. M. daily while symptoms are present, followed by 50 mg. weekly through 1st trimester, or until fetal viability is evident.
Habitual abortion		
1st trim.	10 mg. daily.	50 mg. I.M. weekly.
2nd trim.	20 mg. daily.	100 mg. I.M. q. 2 wks.
3rd trim.	40 mg. daily, through 8th month.	100 mg. I.M. q. 2 wks. through 8th month.
Supplied:	2.5 mg. scored, pink tablets, bottles of 25; 10 mg. scored, white tablets, bottles of 25 and 100.	Sterile aqueous suspension for intramuscular use only. 50 mg. per cc., in 1 cc. and 5 cc. vials.†

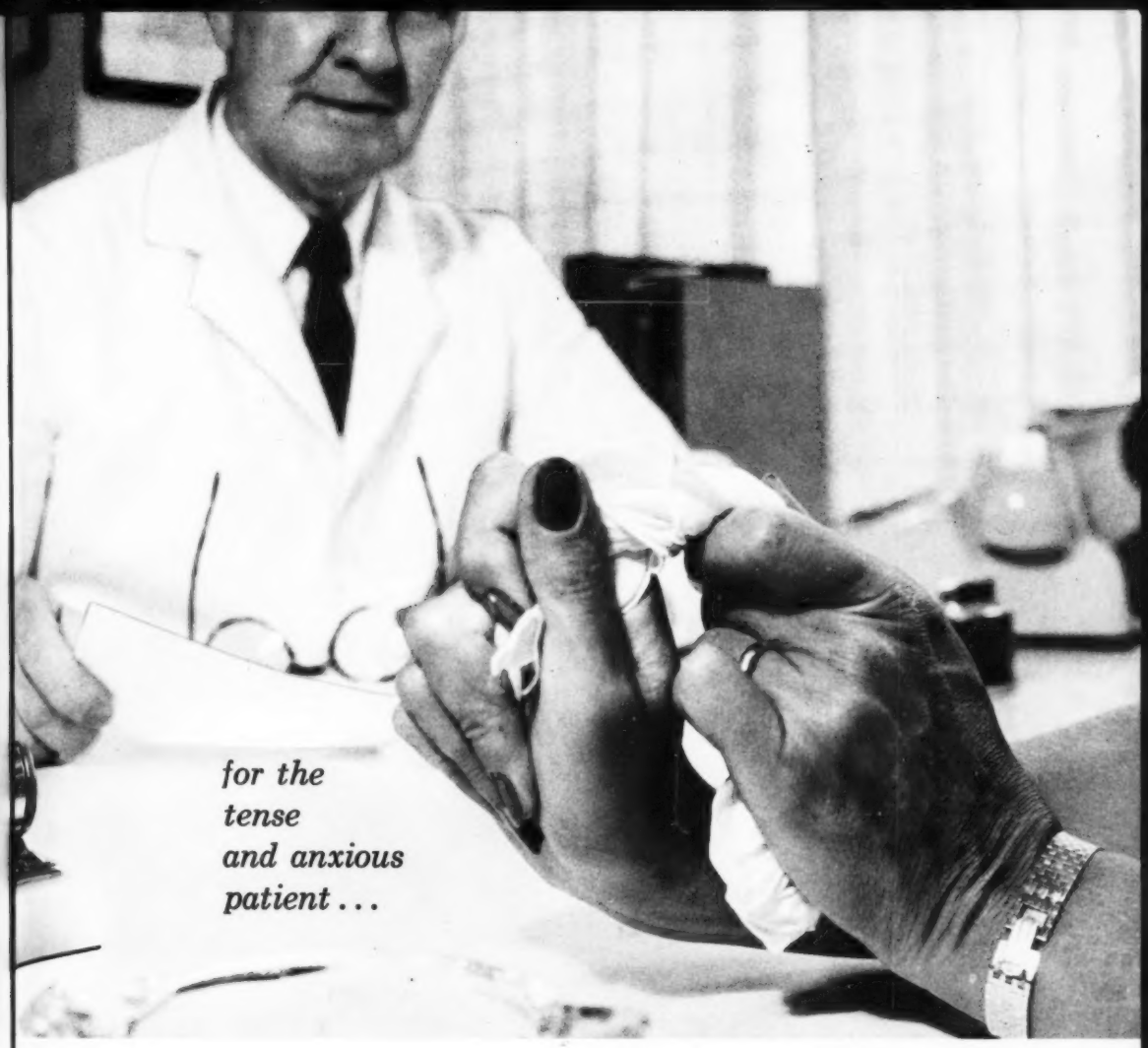
Precautions: Clinically, Provera is well tolerated. No significant untoward effects have been reported. Animal studies show that Provera possesses adrenocorticoid-like activity. While such adrenocorticoid action has not been observed in human subjects, patients receiving large doses of Provera continuously for prolonged periods should be observed closely. Likewise, large doses of Provera have been found to produce some instances of female fetal masculinization in animals. Although this has not occurred in human beings, the possibility of such an effect, particularly with large doses over a long period of time, should be considered.

Provera, administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated.

†Each cc. of Depo-Provera contains: Medroxyprogesterone acetate, 50 mg.; Polyethylene glycol 4000, 28.8 mg.; Polysorbate 80, 1.92 mg.; Sodium chloride, 8.65 mg.; Methylparaben, 1.73 mg.; Propylparaben, 0.19 mg.; Water for injection, q.s.

The Upjohn Company, Kalamazoo, Michigan

*TRADEMARK, REG. U.S. PAT. OFF. **TRADEMARK



a sustained-release tranquilizer that does not cause autonomic side reaction

- **WELL TOLERATED, CONTINUOUS RELIEF** of anxiety and tension for 12 hours with just one capsule – without causing autonomic side reactions and with little or no impairment of mental acuity, motor control or normal behavior.
- **ECONOMICAL** for the patient – daily cost is only a dime or so more than for barbiturates.

Meprospan®-400

400 mg. meprobamate (Miltown®) sustained-release capsules

Usual dosage: One capsule at breakfast lasts all day; one capsule with evening meal lasts all night.

Available: *Meprospan-400*, each blue-topped capsule contains 400 mg. Miltown (meprobamate).
Meprospan-200, each yellow-topped capsule contains 200 mg. Miltown (meprobamate). Both potencies in bottles of 30.

WALLACE LABORATORIES / *Cranbury, N. J.*

In over six years

...for the tense and nervous patient

Miltown is a ***known*** drug and a dependable friend. Its few side effects have been fully reported. ***There are no surprises in store for either the patient or the physician.*** This is why, despite the appearance of "new and different" tranquilizers, meprobamate (Miltown) is prescribed more often than any other tranquilizer in the world.

CM-4649

WALLACE LABORATORIES / *Cranbury, N. J.*

# of clinical use...

Proven
in more than 750 published clinical studies

Effective
for relief of anxiety and tension

Outstandingly Safe

1. simple dosage schedule relieves anxiety dependably – without the unknown dangers of "new and different" drugs
2. does not produce ataxia, stimulate the appetite or alter sexual function
3. no cumulative effects in long-term therapy
4. does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
5. does not muddle the mind or affect normal behavior

Miltown®
meprobamate (Wallace)

Usual dosage: One or two 400 mg. tablets t.i.d.

Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; bottles of 50. Also as MEPROTABS* – 400 mg. *unmarked,* coated tablets; and in *sustained-release* capsules as MEPROSPAN®-400 and MEPROSPAN®-200 (containing respectively 400 mg. and 200 mg. meprobamate).

*TRADE-MARK

CM-4650

I know
it is
effective

The continuing clinical effectiveness of Terramycin therapy derives as always from its proven antibiotic characteristics—rapid absorption; notably wide distribution in body tissues and fluids; high, active urinary concentrations; and a broad anti-infective spectrum embracing even such a troublesome organism as Pseudomonas. Additionally, Terramycin therapy provides the assurance of a 10-year record of exceptional toleration.

Cosa-Terramycin®

OXYTETRACYCLINE WITH GLUCOSAMINE

today's oral *form of Terramycin*

IN BRIEF

Cosa-Terramycin provides oxytetracycline (Terramycin®) with glucosamine for maximum absorption.

INDICATIONS: Because oxytetracycline is effective against both gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain parasites (amebae, pinworms), Cosa-Terramycin is indicated in a great variety of infections due to susceptible organisms, e.g., infections of the respiratory, gastrointestinal, and genitourinary tracts, surgical and soft-tissue infections, ophthalmic and otic infections, and many others.

ADMINISTRATION AND DOSAGE: Adults: 1 Gm. of oxytetracycline daily in four divided doses is usually effective. In *severe* infections, a larger dosage (2-4 Gm. daily) may be indicated. Infants and children: 10-20 mg. of oxytetracycline per lb. of body weight daily. Certain diseases are treated in courses.

SIDE EFFECTS AND PRECAUTIONS: Antibiotics may allow overgrowth of nonsusceptible organisms—particularly monilia and resistant staphylococci. If this occurs, discontinue medication and institute indicated supportive therapy and treatment with other appropriate antibiotics. Aluminum hydroxide gel has been shown to decrease antibiotic absorption and is therefore contraindicated. Glossitis and allergic reactions are rare. There are no known contraindications to glucosamine.

SUPPLIED: *Cosa-Terramycin Capsules,* 250 mg. and 125 mg. Terramycin is also available in: *Cosa-Terrabon® Oral Suspension,* a palatable preconstituted aqueous suspension containing 125 mg. per 5 cc. teaspoonful, bottles of 2 oz. and 1 pint; *Cosa-Terrabon® Pediatric Drops,* a palatable preconstituted aqueous suspension containing 5 mg. per drop (100 mg. per cc.), bottle of 10 cc. with calibrated plastic dropper; and *Terramycin Intramuscular Solution, conveniently preconstituted,* in the new 10 cc. multi-dose vial, 50 mg. per cc., and in 2 cc. prescored glass ampules, containing 100 mg. or 250 mg., packages of 5 and 100. In addition, a variety of other systemic and local dosage forms are available to meet specific therapeutic requirements.

More detailed professional information available on request.

Science for the world's well-being® Pfizer PFIZER LABORATORIES *Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York*

Introducing

"PLEGINE"®

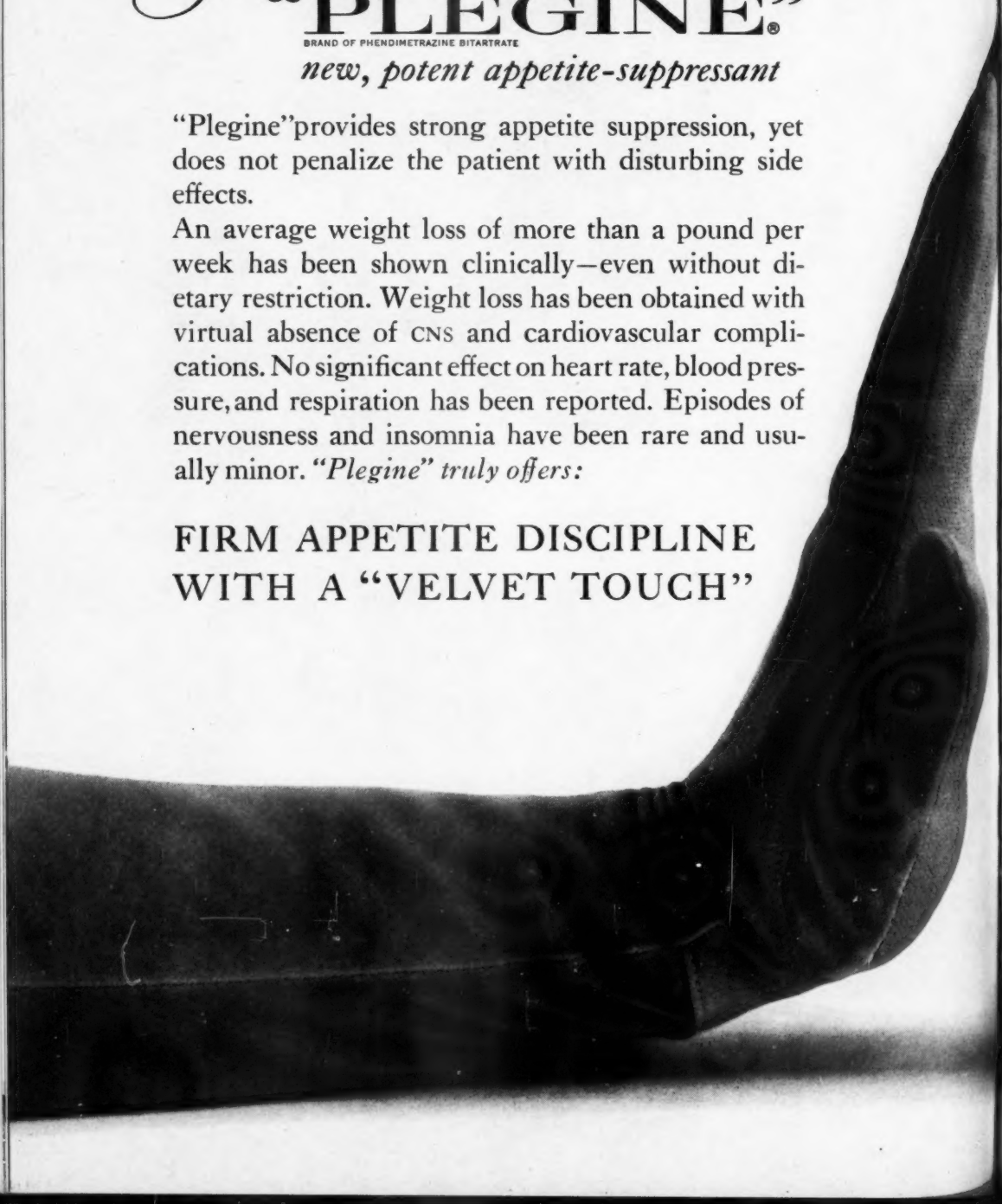
BRAND OF PHENDIMETRAZINE BITARTRATE

new, potent appetite-suppressant

"Plegine"provides strong appetite suppression, yet does not penalize the patient with disturbing side effects.

An average weight loss of more than a pound per week has been shown clinically—even without dietary restriction. Weight loss has been obtained with virtual absence of CNS and cardiovascular complications. No significant effect on heart rate, blood pressure, and respiration has been reported. Episodes of nervousness and insomnia have been rare and usually minor. *"Plegine" truly offers:*

FIRM APPETITE DISCIPLINE WITH A "VELVET TOUCH"



"PLEGINE" *provides unique benefits in the management of obesity*

- suppression of appetite readily and easily achieved
- significant weekly weight loss recorded clinically
- virtually no effects on blood pressure, pulse, and respiration
- low incidence of nervousness and insomnia
- no tolerance reported to date
- high degree of patient acceptability

DOSAGE AND ADMINISTRATION: The usual suggested dosage is 1 tablet b.i.d. or t.i.d., one hour before meals. Dosage, however, should be adjusted to the needs of the patient. In some cases, ½ tablet per dose will suffice; in others, 2 tablets b.i.d. or t.i.d. may be required.

A dietary regimen is advisable in conjunction with appetite-suppressant therapy.

AVAILABILITY: No. 755—Each "Plegine" Tablet contains 35 mg. of Phendimetrazine bitartrate (scored), bottles of 100 and 1,000.

CAUTION AND CONTRAINDICATIONS: No adverse effects on blood pressure, heart rate and respiration have been reported with "Plegine." However, as is true for all medication of this type, "Plegine" is not recommended for patients with coronary disease, severe hypertension, or thyrotoxicosis, and should be used with caution in highly nervous or agitated individuals.

AYERST LABORATORIES
New York 16, N. Y. • Montreal, Canada

6113

for relief of painful leg cramps
of peripheral vascular disease

VASODILAN

Isoxsuprine hydrochloride, Mead Johnson

myo- -vascular relaxant

increases deep peripheral circulation by direct action
...without troublesome side effects

examination of postexercise pedal pulses key to earlier detection of peripheral vascular disease

IPLE OFFICE TEST* EXPEDITES TREATMENT

Palpating pedal pulsation at rest.

A recent report* shows that peripheral arteriosclerosis as a cause of intermittent claudication is frequently overlooked because early in the disease the patient may have adequate pedal pulses if he is examined only at rest.

13 patients with fatigue, aching or severe leg mps, all of whom had readily palpable pedal ses at rest, DeWeese* demonstrated disappear- e of these pulses following sufficient exercise to ng on pain. In his test, patients ran in place at 140 to 160 steps a minute until claudication occurred. A possible explanation of this phenomenon "...is based on the shunting of the insufficient blood supply to smaller, vasodilated arteries so that weakened pulsations are observed in the larger arteries."*

ercising patient prior to post-ercise palpation of pulses.

sed on his findings, DeWeese recommends "...that exercise test be performed on any patient with symptoms suggestive of intermittent claudication who has palpable pedal pulses [at rest], before obstructive atherosclerosis is ruled out as a cause of the symptoms."*

texercise shunting of blood into dilated collaterals.

Awareness of this phenomenon, with routine performance of the exise test, will undoubtedly help increase early diagsis of peripheral vascular disease. Consequently, eatment can be instituted sooner, improving the elihood of a favorable response to therapy.

Weese, J. A.: New England J. Med. *262*:1214-1217 (June 16) 1960.

VASODĪLAN IS CLINICALLY EFFECTIVE[1-3]

"Isoxsuprine hydrochloride [VASODĪLAN] was administered orally for a median period of seven months to 46 patients suffering from arteriosclerosis obliterans. Objective improvement could be demonstrated in...[about 85 per cent] of these."[1]

"Isoxsuprine [VASODĪLAN] was used in the management of arteriosclerosis obliterans in 46 patients...." The average "maximal walking distance, measured in 41 patients, more than doubled...during isoxsuprine [VASODĪLAN] therapy...."[2]

"With strictly a clinical office approach, isoxsuprine [VASODĪLAN] was used in the treatment of 100 patients with peripheral vascular disorders. Definite clinical improvement was obtained in 89 per cent of these patients."[3]

VIRTUALLY NO SIDE EFFECTS WITH ORAL DOSAGE[1-3]

In a study of 100 patients, "On an oral dose...no side effects have occurred."[3] "With oral administration, there are no contraindications."[2] "There were no significant side-effects...suggestive of the existence of contraindications."[1]

Contraindications: There are no known contraindications to oral administration of VASODĪLAN in recommended doses.

Cautions: VASODĪLAN should not be given immediately postpartum or in the presence of arterial bleeding. Parenteral administration is not recommended in the presence of hypotension or tachycardia. Intravenous administration is not recommended because of the increased likelihood of side effects.

Side effects: Few side effects occur when given in recommended oral doses. Occasional palpitation and dizziness can usually be controlled by dosage adjustment. Single intramuscular doses of 10 mg. or more may result in hypotension or tachycardia.

Dosage and administration: Oral—10 to 20 mg. (1 to 2 tablets) t.i.d. or q.i.d.; I.M.—5 to 10 mg. b.i.d. or t.i.d.

Supplied: 10 mg. tablets in bottles of 100; in 2 cc. ampuls containing 10 mg. (5 mg./cc.) for intramuscular use, boxes of 6.

For complete details on indications, dosage, administration, and clinical background of VASODĪLAN, see the brochure of this product available on request from Mead Johnson Laboratories, Evansville 21, Indiana.

References: (1) Samuels, S. S., and Shaftel, H. E.: J.A.M.A. *171*:142-144 (Sept. 12) 1959. (2) Kaindl, F.; Samuels, S. S.; Selman, D., and Shaftel, H.: Angiology *10*:185-192 (Aug.) 1959. (3) Clarkson, I. S., and Le Fere, D. M.: Angiology *11*:190-192 (June) 1960.

Mead Johnson Laboratories

Symbol of service in medicine

Many **MIGRAINE** attacks can be **stopped at the start** by the prompt use of...

'MIGRAL'®

Advantage

'MIGRAL' permits maximum ergotamine therapy with the first dose —because the 'MIGRAL' formula includes the proved antiemetic, cyclizine hydrochloride, to counteract the tendency to nausea and vomiting.

Dosage

'MIGRAL' should be taken immediately at the start of a migraine attack, and the effective dosage should be determined on an individual basis. When the total dosage necessary to stop an attack has been determined, that amount should be taken as initial dosage in subsequent attacks.

In general, 2 to 4 'MIGRAL' tablets taken at the first sign of an attack will terminate a headache by preventing progression to the vasodilation stage. If treatment is not started sufficiently early to achieve this result, an additional 1 or 2 tablets should be administered every half hour until the patient is relieved, or until a total dosage of 6 tablets has been taken.

Caution

It is recommended that not more than 6 tablets be taken during a single attack, nor more than 10 tablets per week.

Each sugar-coated 'MIGRAL' tablet provides:

Ergotamine Tartrate	1 mg.
'Marezine'® brand Cyclizine Hydrochloride	25 mg.
Caffeine	50 mg.

In bottles of 20 and 100 tablets.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

when patients complain of gas or bloat...

new

MYLICON®

MYLICON relieves the gastrointestinal distress produced by entrapped gas. MYLICON's defoaming action changes the surface tension of gas bubbles, permitting them to coalesce. This gas is released and eliminated by belching or passing flatus. MYLICON is physiologically inert, nontoxic.

Gas entrapment and distention can result from Spastic Colitis, Aerophagia, Postoperative Gas, Postgastrectomy Syndrome, Hyperacidity, Hiatus Hernia, Diverticulitis, Gastric and Duodenal Ulcers.

Pleasant tasting, soft chewable tablets can be taken without water.

One white scored tablet contains:
Methylpolysiloxane, a silicone.....40 mg.

DOSAGE: one tablet after each meal and at bedtime.

SUPPLIED: bottles of 100 and 500 tablets at all pharmacies.

References: "Intestinal Gas and Bloating; Treatment with Methylpolysiloxane," Am. Pract. & Dig. of Treat., 11:52. (Jan.) 1960.

"Use of Silicone in the Treatment of Intestinal Gas and Bloating," J.A.M.A., 174:2052, (Dec. 17) 1960.

also *NEW* **MYLICON® DROPS**
for infant colic caused by excessive air swallowing or inability to belch or pass flatus.

MYLICON DROPS (0.3 cc. to 0.6 cc.) can be given directly from the dropper or added to each feeding.

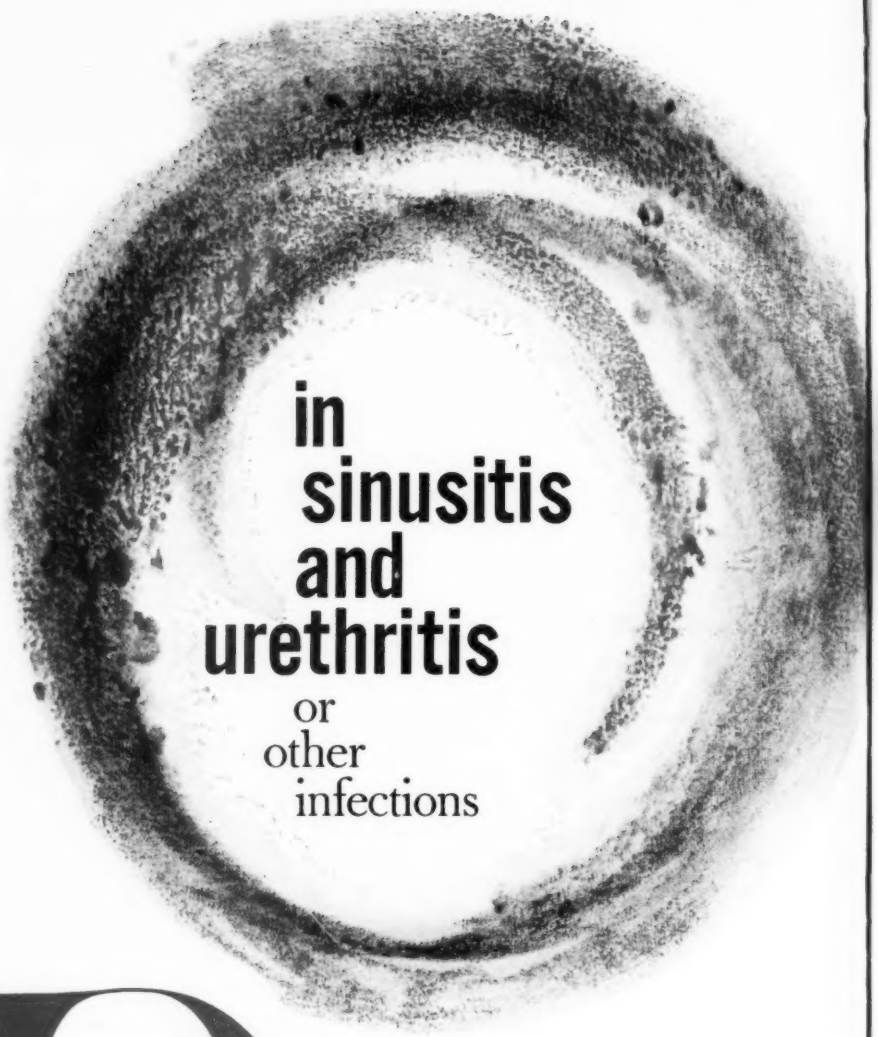
Each 0.6 cc. represents 40 mg. of methylpolysiloxane, equivalent to one MYLICON tablet.

Available at all pharmacies in bottles of 30 cc. of drops.

Stuart

THE STUART COMPANY
PASADENA, CALIFORNIA

11881/4100



DECLO

antibiotic therapy wit n a

CAPSULES, 150 mg., 75 mg. *Dosage:* Average infections—150 mg. four times daily. Severe infections—Initial dose of 300 mg., then 150 mg. every six hours.

PEDIATRIC DROPS, 60 mg./cc. in 10 cc. bottle with calibrated, plastic dropper. *Dosage:* 1 to 2 drops (3 to 6 mg.) per pound body weight per day—divided into four doses.

SYRUP, 75 mg./5 cc. teaspoonful (cherry-flavored). *Dosage:* 3 to 6 mg. per pound body weight per day—divided into four doses.

PRECAUTIONS—As with other antibiotics, DECLOMYCIN m occasionally give rise to glossitis, stomatitis, proctitis, nau diarrhea, vaginitis or dermatitis. A photodynamic reactio sunlight has been observed in a few patients on DECLOMY Although reversible by discontinuing therapy, patients sh avoid exposure to intense sunlight. If adverse reaction or id syncrasy occurs, discontinue medication.

Overgrowth of nonsusceptible organisms is a possibility w DECLOMYCIN, as with other antibiotics, and demands that patient be kept under constant observation.

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

aga
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with added measure of protection

MYCIN®

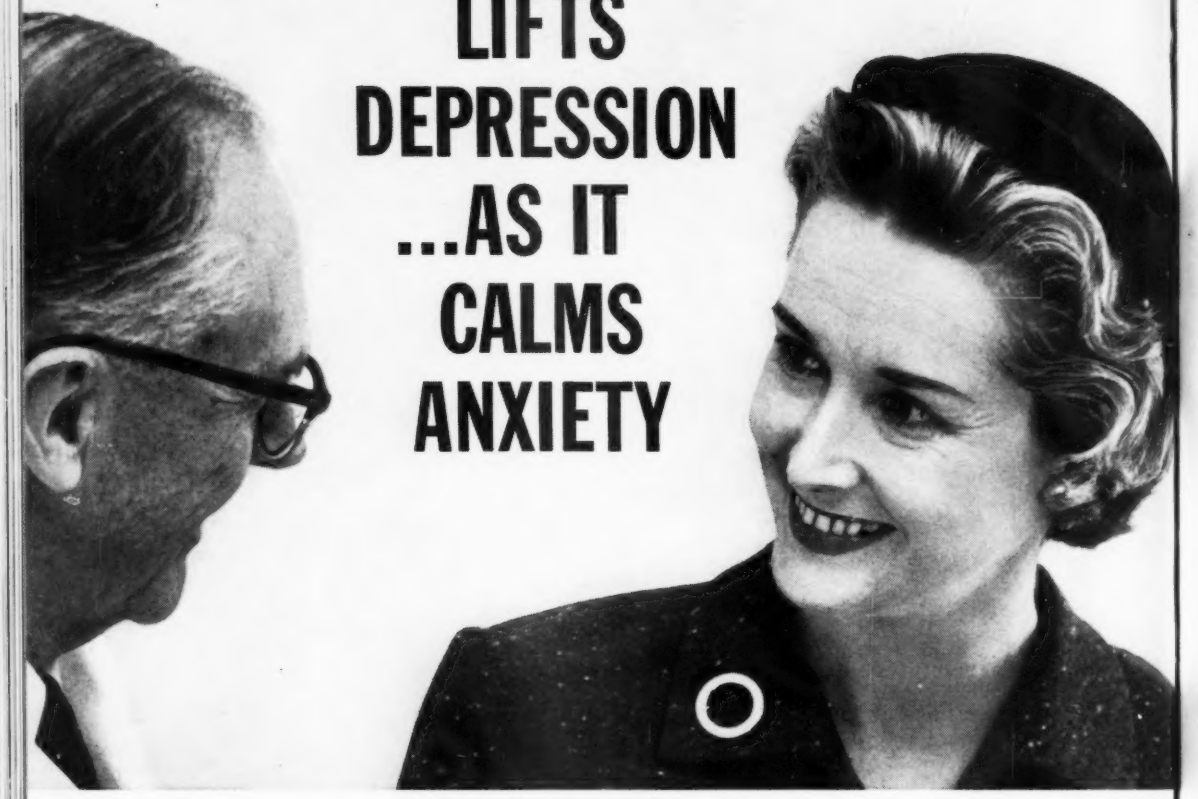
DEMETHYLCHLORTETRACYCLINE LEDERLE

against relapse—up to 6 days' activity on 4 days' dosage

against secondary infection—sustained high activity levels

against "problem" pathogens—positive broad-spectrum antibiosis

LIFTS DEPRESSION ...AS IT CALMS ANXIETY



"I feel like my old self again!" Thanks to your balanced Deprol therapy, her depression has lifted and her mood has brightened up – while her anxiety and tension have been calmed down. She sleeps better, eats better, and normal drive and interest have replaced her emotional fatigue.

Brightens up the mood, brings down tension

Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines. While energizers and amphetamines may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression and emotional fatigue.*

These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety – a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

Acts rapidly – you see improvement in a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – *often within a few days.* Thus, the expense to the patient of long-term drug therapy can be avoided.

Acts safely – no danger of liver or blood damage. Deprol does not cause liver toxicity, anemia, hypotension, psychotic reactions or changes in sexual function – frequently reported with other drugs.

▲Deprol▲®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets. Write for literature and samples.

CD-4524 WALLACE LABORATORIES / *Cranbury, N. J.*

YOUR FINANCES

FINANCIAL PLANNING FOR THE MEDICAL PRACTITIONER

Bonds for investment and speculation . . . an introduction to an important but less well-known field of investment.

prepared by

CEDRIC CAMPBELL

for

Postgraduate Medicine

June 1961

As a form of investment, bonds for years have been the almost exclusive preserve of large financial institutions or of ultra-conservative wealth.

As a medium for speculation, they have historically attracted only the highly sophisticated, highly venturesome elements of the financial community.

Despite the general public's haziness about bonds, they are today fast acquiring new adherents – both as a field for investment and for rapid and substantial capital appreciation.

Some of the factors behind this are: a) bond yields are rising as stock yields go down; b) some bonds offer big tax-saving benefits, and c) growing awareness of the speculative opportunities in bonds.

* * * * *

To understand why there is still so little familiarity with bonds – even on the part of many financial professionals – is to understand why they remain so widely neglected . . . and why they offer many opportunities for capital appreciation and income.

Two of the primary causes: 1) Bonds pay far lower commissions to brokers (a typical $5,000 stock sale brings the broker about $45; the same dollar-sale in bonds nets him only $12.50). 2) By far the greater part of all promotion and publicity (including the New York Stock Exchange itself) deals with the advantages of stocks.

More bluntly, bonds aren't always easy to buy. (Case in point: There are less than 20 Government bond dealers in the country.) Most brokers, if pressed, will help you – but, in many cases, they'll have to go in for a bit of self-education on the subject before knowing the best way to go about it.

But more on that later. The advantages in bonds will be more clear from exploring this basic question:

WHAT IS A BOND?

A bond is a promise to pay . . . an evidence of a stated amount of debt . . . akin to, but far more handsomely printed than, a promissory note.

It may be issued by the government, by a municipality, by private corporations. Ordinarily its face value is $1,000, and its period of maturity is 20 years or more. It pays a guaranteed interest ranging from 4%, in the case of most government bonds, to 6% or more in the case of most corporate bonds. Interest payments usually come in the form of perforated coupons, dated with each interest due date, attached to the bond.

> Thus a $1,000 5% bond will pay the investor $50 interest a year for each year of its life, plus the $1,000 face value on maturity . . . or a total of $2,000 over a 20-year period.

Bonds may be "secured" by income-producing properties; e.g., in the case of certain municipals, toll highways and bridges. With a government, its bond is only as good as its word. Corporate bonds are backed by the assets and earnings of the issuing company.

Unsecured bonds are called "debentures" - liens on the credit of the issuer, rather than liens on a specific piece of property.

> As a general rule, the lower the interest rate, the sounder, less speculative the bond.
>
> Governments (U.S.) are almost always rated triple-A, pay the lowest interest. But interest from government bonds is exempt from state taxes. Similarly, interest from municipal bonds is exempt from federal taxes.

This latter feature of bonds is one of the charms they hold for high-bracket investors. In municipal bonds, for example, a tax-exempt yield of 5% is equivalent to a 10% taxable yield to an investor in the 50% bracket.

* * * * *

Part of the mystery surrounding bonds is probably due to the way they are traded. Stock Exchange quotations for bonds, for example, are not expressed in terms of direct dollar selling prices, as in the case of stocks. Rather, they are quoted in percentages of a par of $1,000. A typical bond price quotation might read:

> Am T & T 5s 83.....105¾

Translated, this means that an issue of American Telephone and Telegraph bonds carrying an interest coupon of 5%, maturing in 1983, sold at 105¾ of par, or $1,057.50.

One further basic type of bond warrants discussion: THE CONVERTIBLE.

Automotively speaking, it couldn't have been better named: A convertible bond may be exchanged for the same company's common stock whenever the holder decides common stock offers a better ride for his money.

Consider Philco convertible bonds maturing 1984 and paying 4¼. These bonds are convertible before April 15, 1969 into 30 shares of Philco's common stock. When the Philco 4¼ bond was selling for a total of $1,170, if this had been converted into the common stock then selling at 34, the investor would have had a value of only $1,020. However, possession of the bond would have given him an option or call on the common stock for a 10-year period, and he would have paid a premium of only $150 per bond for the privilege. If, therefore, he were optimistic about the growth possibilities for Philco, purchase of the bonds would have enabled him to share in any future price appreciation at the same time that he enjoyed the safer shelter of a bond. (Note, however, that because of the relationship between convertible bonds and the company's common stock, there is both more risk and greater fluctuation in the convertible bond than in the nonconvertible bond.)

* * * * *

With this brief summary out of the way, let's consider the possibilities of bonds as investments or speculations for the practitioner.

BONDS AS INVESTMENTS

You can't beat bonds for <u>safety</u> – as an almost hard and fast rule. (There are exceptions, which will be treated later under speculation.)

Safest are treasury bonds (4% interest yield), followed in descending order by what are called high-grade bonds (4⅛%), medium-grade bonds (5%) and low-grade bonds (6%).

In bonds, as in everything else financial, you pay your money and take your choice. If it's <u>tax-exempt income</u> that interests you most, you buy either Governments or municipals (depending on which form of tax exemption you seek).

If it's <u>maximum income</u> you want (regardless of tax exemption) you look for bonds with a high coupon and selling at a discount from par.

And if it's <u>safety plus a higher yield</u> than Treasury bonds, you'll look first to the blue chips, the country's top industrial and business enterprises.

In any case, once you've passed beyond the curiosity stage, the best procedure is to get a rating on the bond you have in mind. Any broker or dealer can get this for you from Moody's, Standard & Poor or Fitch, the three principal rating services – without cost. <u>(N.B. This may be all he knows about bonds, but he'll know this.)</u>

Moody's gives 9 ratings in descending order from Aaa to C; S&P gives 11, and Fitch 12. In general, ratings are a pretty good indication of the reliability of the listed bond. Also in general, bonds in the top four categories of ratings will prove sound investments.

When it comes to buying, your own broker or your bank can do this for you.

BONDS AS SPECULATIONS

There are many ways to speculate in bonds; some simple, some fantastically intricate (stay away from these!) and some, while strictly legal, are liable to be outlawed by the U.S. Department of Internal Revenue any day.

The simple category includes defaulted bonds of certain foreign governments. Many investors made tremendous profits in German, Japanese and Italian bonds after World War II. At the moment, some South American Governments and certain Yugoslavian and Greek issues may be attractive.

Way out on the periphery of speculation are bonds of some Iron Curtain countries, notably Czechoslovakia, Poland and China. Polish bonds have been actively traded at around 12, and China Government Railway 5s of 1951 at about 5. If either of the last two countries should become more independent of the USSR and begin honoring its bond commitments – two admittedly very large IFs – the reward could be tremendous. But the risks, obviously, are large too.

As a rule, biggest speculative returns are from bonds selling at discounts and paying a high coupon – the hope is that ultimately they'll climb back closer to their par value. Quite a few railroads are in this category now – and as some states move to relieve the crisis brought by the commuter situation, they could turn out to be smart buys for capital appreciation as well as for high income.

* * * * *

IN THE NEXT ISSUE: Which Bonds For You? Specific Examples Illustrating the Place of Bonds in the Portfolio.

* * * * *

Additional reading on material covered in this article might include: "Investments," George W. Dowrie and Douglas R. Fuller, John Wiley & Sons, Inc., New York; "R. H. M. Convertible Survey," R.H.M. Associates, New York and "Investment Analysis and Management," Lester V. Plum and Joseph M. Humphrey, Richard D. Irwin, Inc., Chicago.

* * * * *

Information contained in these articles is as accurate as careful checking and reliable sources can make it, but cannot, of course, be guaranteed.

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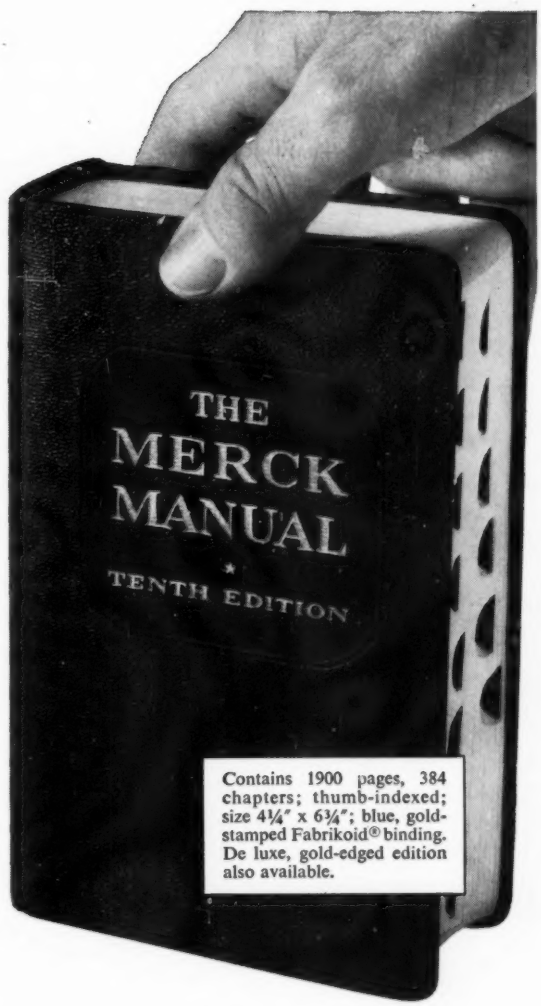

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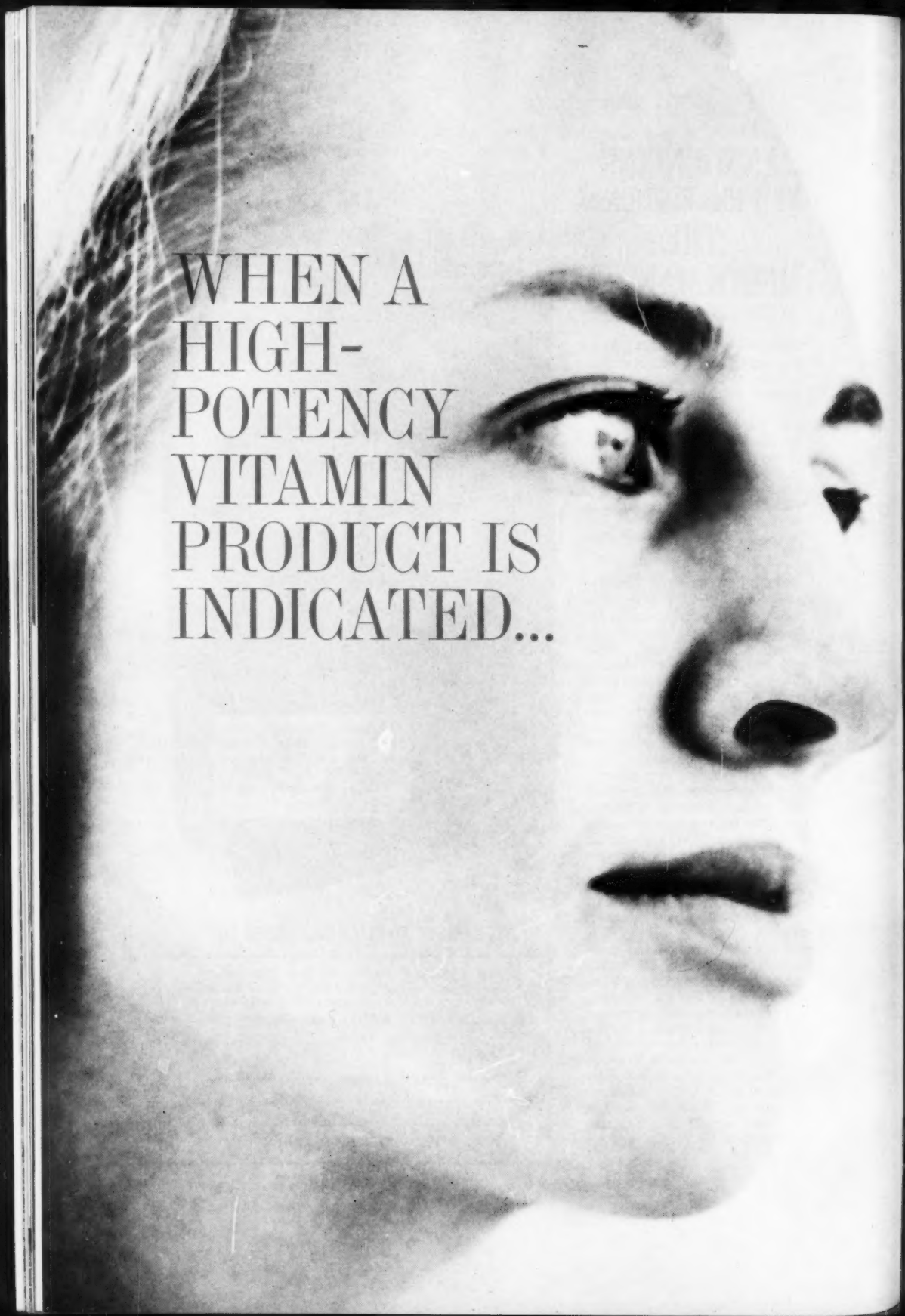
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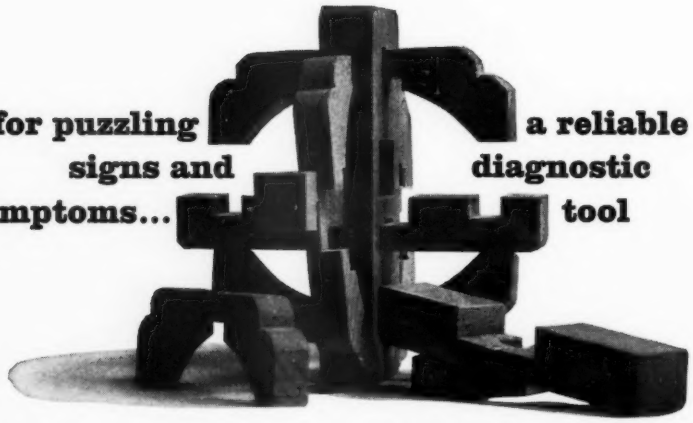

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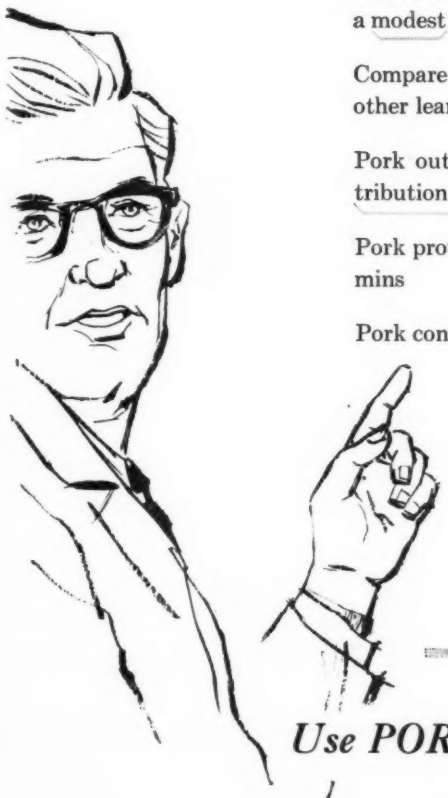

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1. Leverton, R.M., and Odell, G.V.: The Nutritive Value of Cooked Meat, Oklahoma Agricultural Experiment Station, Oklahoma State University, Miscellaneous Publication MP-49, 1958.

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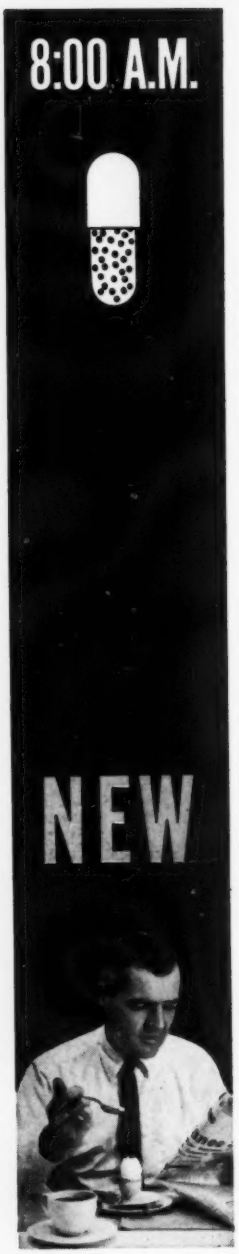

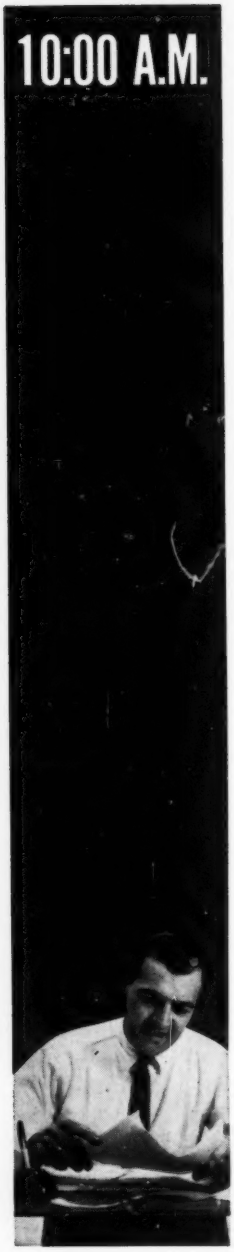

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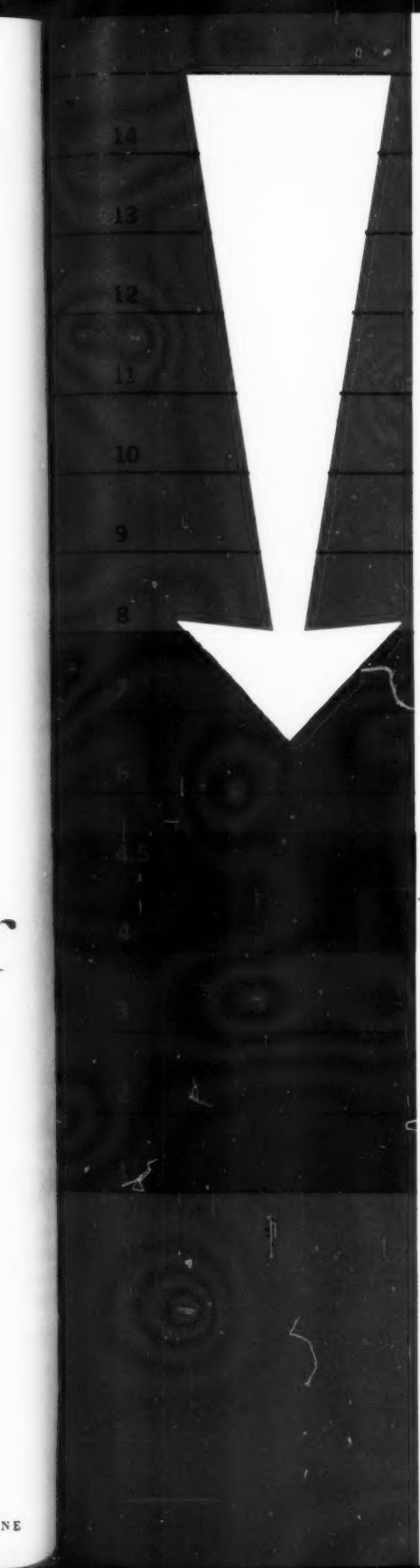

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The *buffered* acid douche solution of Massengill Powder (pH 3.5-4.5) resists neutralizing. And this normal, low pH is maintained for 4 to 6 hours in ambulant patients . . . and as long as 24 hours in recumbent patients.

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3 PENETRATES VAGINAL MUCOSAL FOLDS

Low surface tension of Massengill Powder solution is 50 dynes/cm. (vinegar is 72 dynes/cm.). This enables it to penetrate and cleanse folds of the vaginal mucosa. And this low surface tension makes cell walls of infecting organisms more susceptible to therapy.

4 WON'T DEVELOP RESISTANT STRAINS

Because normal pH is restored, normal environment is created . . . pathogens can't thrive . . . resistant strains can't develop as with antibiotics.

5 IS ACCEPTABLE TO PATIENTS

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Disease:
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Rheumatoid arthritis

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In severe or moderately severe cases, initial dosage of Medrol tablets is 8 to 16 mg. daily; maintenance dosage ranges from 4 to 12 mg. daily, adjusted stepwise every 5 to 10 days in accordance with response. In children, and also in adults with moderate disease, both initial and maintenance dosage is Medrol 4 to 8 mg. daily.

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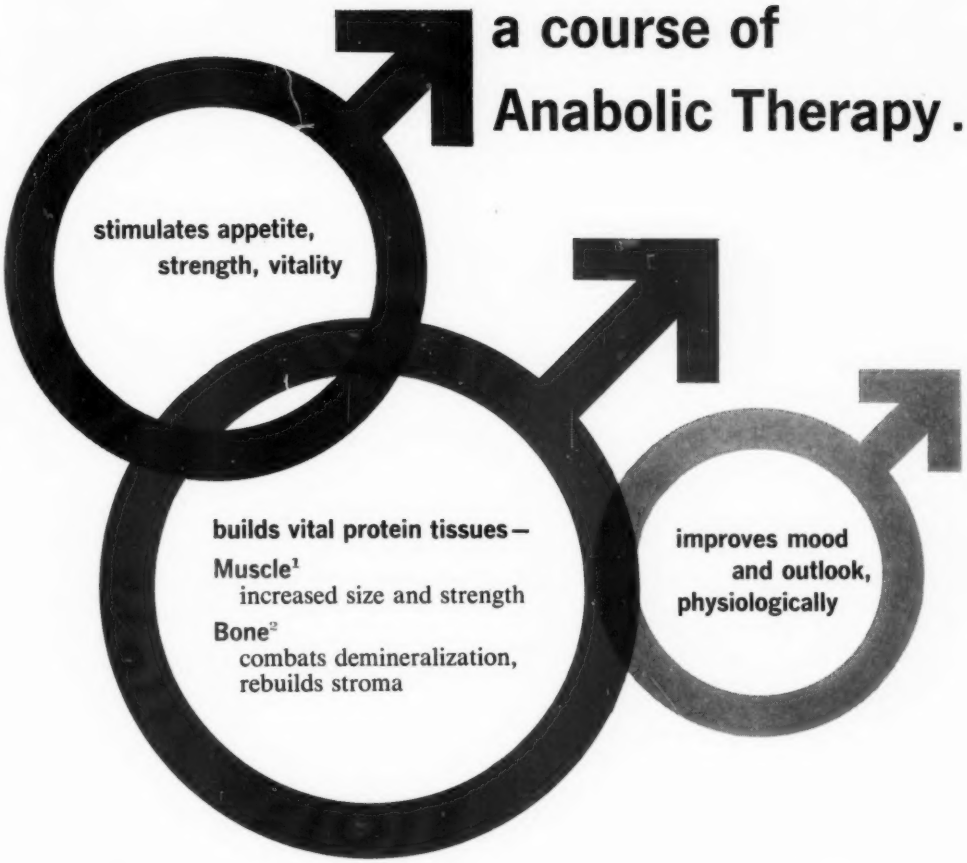

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1. Osol, A. and Farrar, G. E., Jr.: The Dispensatory of the U.S.A., ed. 25, J. B. Lippincott, Philadelphia, 1955, p. 1392.
2. Best, C. H. and Taylor, N. B.: The Physiologic Basis of Medical Practice, ed. 7, The Williams and Wilkins Co., Baltimore, 1961, p. 1104.

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Oral therapy with DIABINESE can help assure more adequate blood-sugar control in many maturity-onset diabetics, including certain patients now poorly controlled by diet alone, some patients on insulin, and many who escape control on previous oral therapy.

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In patients with maturity-onset diabetes whose blood sugar remains elevated despite weight and/or caloric control, DIABINESE is frequently effective in doses of 100 to 250 mg. a day. Further, unlike insulin, DIABINESE has not been reported to increase appetite, and residual capacity for endogenous beta cell activity is stimulated. Thus, DIABINESE combined with dietary regulation will often ensure more satisfactory control than "diet alone."

Diabinese and the insulin patient

DIABINESE has proved to be an effective replacement for insulin among maturity-onset patients needing 40 units or less per day. This application of DIABINESE is especially valuable in patients who should not be exposed to the hazards and inconvenience of self-administered injection—those with poor eyesight, the infirm and elderly, and the emotionally disturbed. Transfer from insulin to DIABINESE in proper dosage lessens the risk of hypoglycemia, and may enable certain patients to resume occupations where insulin shock is considered dangerous.

In selected patients in whom insulin requirements have become quite high, combined therapy with DIABINESE sometimes permits reduction of insulin dosage and helps to improve control.[3] Patients with insulin resistance may sometimes be similarly helped by replacement of part of the daily insulin dosage.[4]

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Continuous control in suitable candidates for sulfonylurea therapy is more likely to be achieved with DIABINESE. According to the A.M.A. Council on Drugs,[5] observations indicate that "on an equivalent dose and blood level basis, chlorpropamide has a somewhat greater therapeutic effect than has tolbutamide." This therapeutic superiority is reflected in the results of clinical observations like those of Fineberg,[6] who compared the effect of DIABINESE in 50 patients with the effect of tolbutamide in 35 patients. He concluded that "chlorpropamide produced satisfactory control of the diabetes in almost twice as great a percentage (76 versus 43 per cent) of patients than did tolbutamide, and excellent control in more than twice as great a percentage (74 versus 31 per cent)."

1. Johnsson, S.: Diabetes 9:1, 1960. 2. El Mahallawy, M. N., and Sabour, M. S.: J.A.M.A. 173:1783, 1960. 3. Editorial: Brit. M. J. 1:188, 1961. 4. Duncan, L. J. P., and Baird, J. D.: Pharmacol. Rev. 12:91, 1960. 5. A.M.A. Council on Drugs: New and Nonofficial Drugs, 1961, Philadelphia, Lippincott, 1961, p. 657. 6. Fineberg, S. K.: J. Am. Geriat. Soc. 8:441, 1960.

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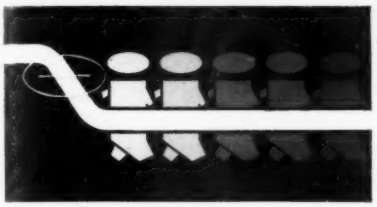

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DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Like insulin, DIABINESE dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

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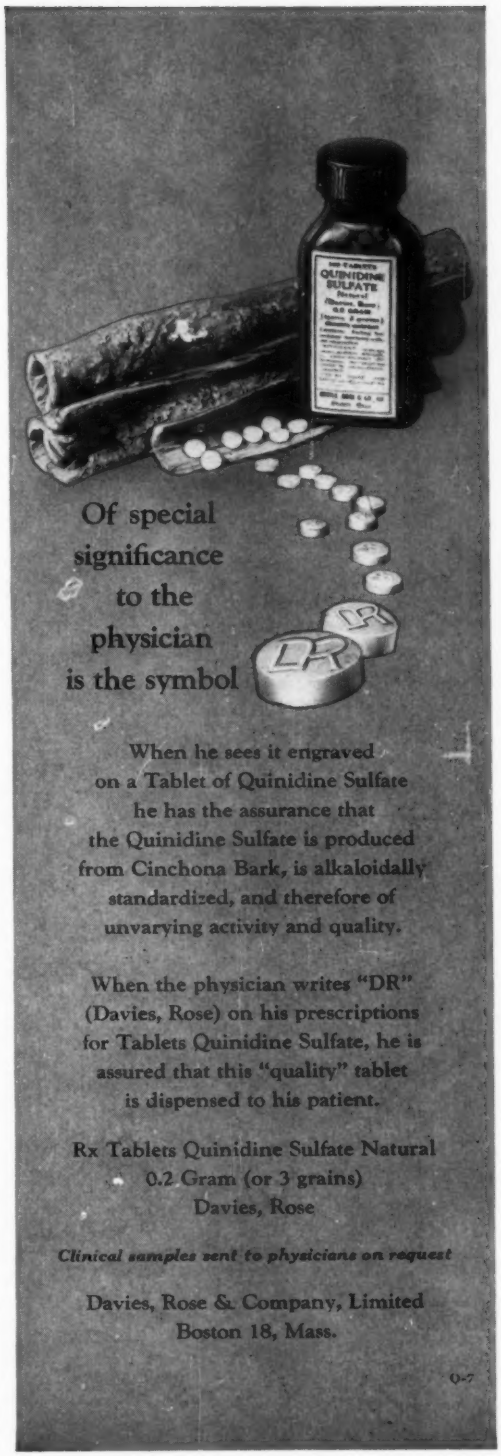
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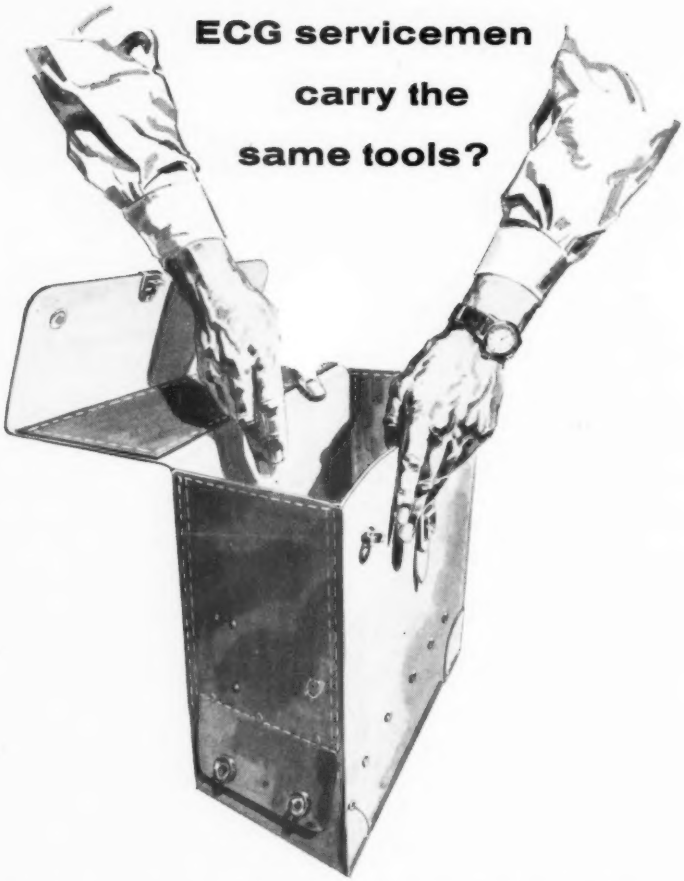

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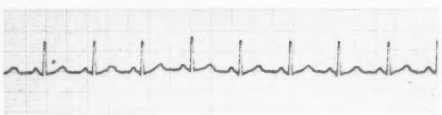

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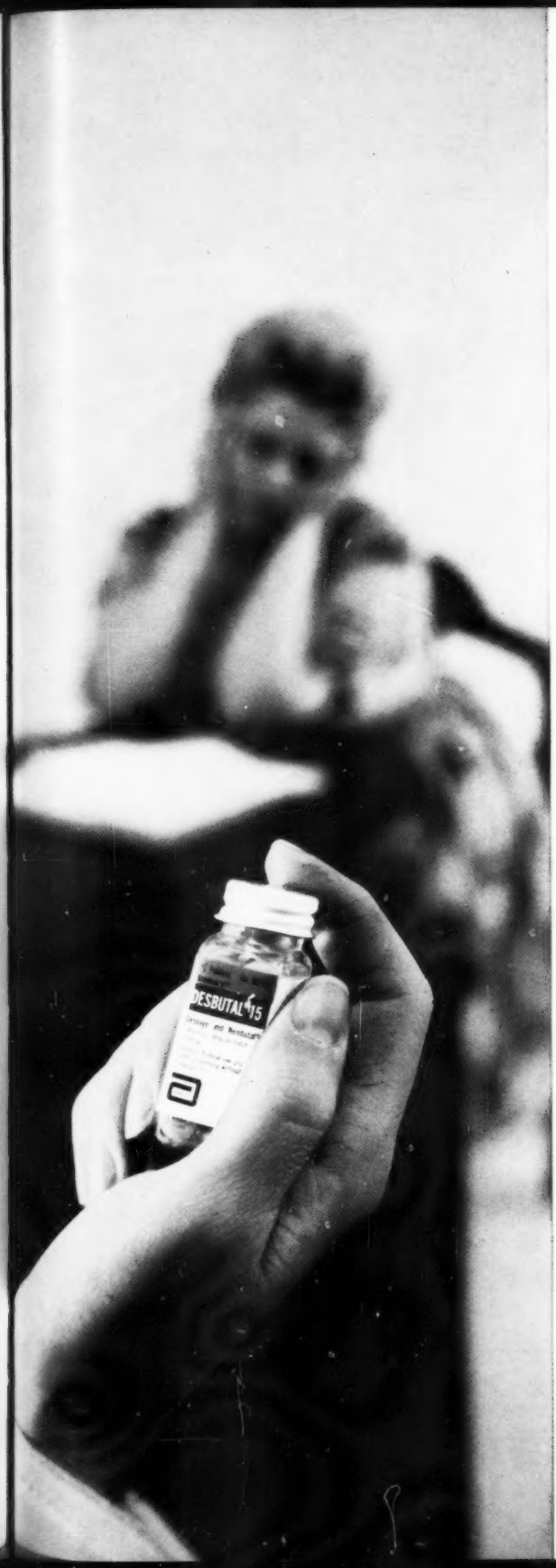

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